L Number	Hits	Search Text	DB	Time stamp
1	357	(514/418).CCLS.	USPAT; US-PGPUB	2003/10/09 15:04
2	349	(548/486).CCLS.	USPAT; US-PGPUB	2003/10/09 15:04
3	591	((514/418).CCLS.) ((548/486).CCLS.)	USPAT; US-PGPUB	2003/10/09 15:04
4	44	(((514/418).CCLS.) ((548/486).CCLS.)) and migraine	USPAT; US-PGPUB	2003/10/09 15:04
7	68	"3" and "3" adj fluoro$10	USPAT; US-PGPUB	2003/10/09 15:06
8	7	((((514/418).CCLS.) ((548/486).CCLS.)) and migraine) and ("3" and "3" adj fluoro$10)	USPAT; US-PGPUB	2003/10/09 15:06

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1611txm

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 09	CA/CAplus records now contain indexing from 1907 to the present
NEWS	4	Jul 15	Data from 1960-1976 added to RDISCLOSURE
NEWS	5	Jul 21	Identification of STN records implemented
NEWS	6	Jul 21	Polymer class term count added to REGISTRY
NEWS	7	Jul 22	INPADOC: Basic index (/BI) enhanced; Simultaneous Left and Right Truncation available
NEWS	8	AUG 05	New pricing for EUROPATFULL and PCTFULL effective August 1, 2003
NEWS	9	AUG 13	Field Availability (/FA) field enhanced in BEILSTEIN
NEWS	10	AUG 15	PATDPAFULL: one FREE connect hour, per account, in September 2003
NEWS	11	AUG 15	PCTGEN: one FREE connect hour, per account, in September 2003
NEWS	12	AUG 15	RDISCLOSURE: one FREE connect hour, per account, in September 2003
NEWS	13	AUG 15	TEMA: one FREE connect hour, per account, in September 2003
NEWS	14	AUG 18	Data available for download as a PDF in RDISCLOSURE
NEWS	15	AUG 18	Simultaneous left and right truncation added to PASCAL
NEWS	16	AUG 18	FROSTI and KOSMET enhanced with Simultaneous Left and Righ Truncation
NEWS	17	AUG 18	Simultaneous left and right truncation added to ANABSTR
NEWS	18	SEP 22	DIPPR file reloaded
NEWS	19	SEP 25	INPADOC: Legal Status data to be reloaded
NEWS	20	SEP 29	DISSABS now available on STN

NEWS EXPRESS	OCTOBER 01 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:26:16 ON 09 OCT 2003

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 13:26:32 ON 09 OCT 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 OCT 2003 HIGHEST RN 601453-92-3
DICTIONARY FILE UPDATES: 8 OCT 2003 HIGHEST RN 601453-92-3

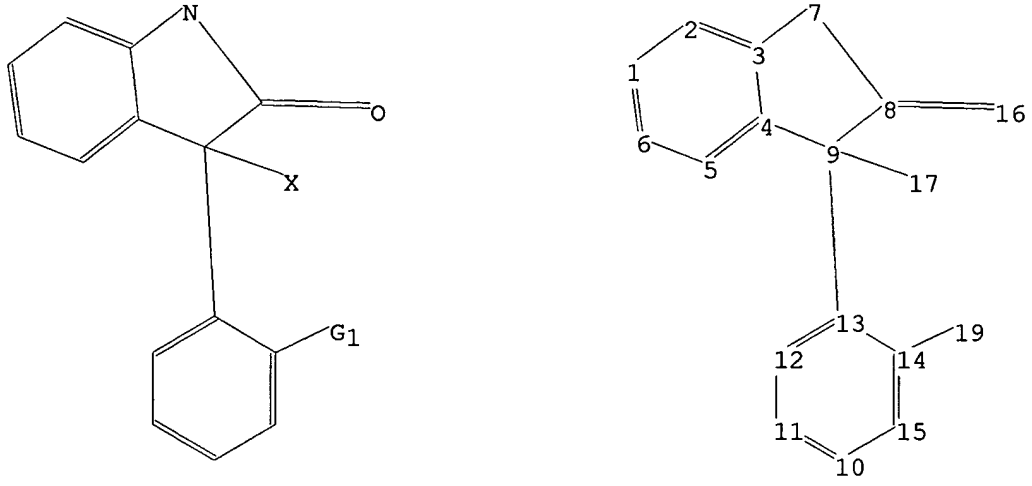
TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

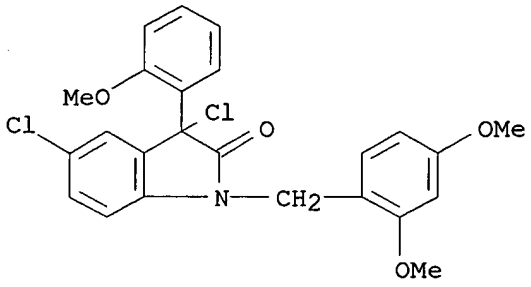
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading C:\Program Files\Stnexp\Queries\10075703.str



chain nodes :

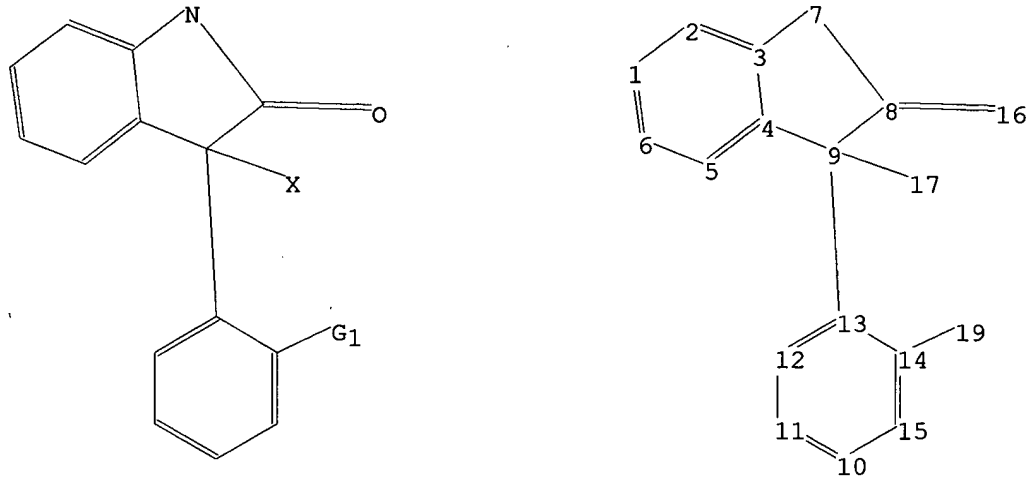
```
16  17  19
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12  13  14  15
chain bonds :
8-16  9-13  9-17  14-19
ring bonds :
1-2  1-6  2-3  3-4  3-7  4-5  4-9  5-6  7-8  8-9  10-11  10-15  11-12  12-13  13-14
 14-15
exact/norm bonds :
3-7  4-9  7-8  8-9  8-16  14-19
exact bonds :
9-13  9-17
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  10-11  10-15  11-12  12-13  13-14  14-15
isolated ring systems :
containing 1 : 10 :


G1:O,S

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:CLASS  17:CLASS  19:CLASS



L1      STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 13:26:48 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      3 TO ITERATE

100.0% PROCESSED       3 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            3 TO      163
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 13:26:58 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     74 TO ITERATE

100.0% PROCESSED      74 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

L3            1 SEA SSS FUL L1

=> d scan

L3   1 ANSWERS   REGISTRY  COPYRIGHT 2003 ACS on STN
IN   2H-Indol-2-one, 3,5-dichloro-1-[(2,4-dimethoxyphenyl)methyl]-1,3-dihydro-3-
     (2-methoxyphenyl)- (9CI)
MF   C24 H21 Cl2 N O4
```



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=>
Uploading C:\Program Files\Stnexp\Queries\10075703.str



chain nodes :
16 17 19
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
chain bonds :
8-16 9-13 9-17 14-19
ring bonds :
1-2 1-6 2-3 3-4 3-7 4-5 4-9 5-6 7-8 8-9 10-11 10-15 11-12 12-13 13-14
14-15
exact/norm bonds :
3-7 4-9 7-8 8-9 8-16 14-19
exact bonds :
9-13 9-17
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 10-11 10-15 11-12 12-13 13-14 14-15
isolated ring systems :
containing 1 : 10 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:CLASS 19:CLASS

L4 STRUCTURE UPLOADED

=> s l4
SAMPLE SEARCH INITIATED 13:28:10 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 3 TO ITERATE

100.0% PROCESSED 3 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 3 TO 163
PROJECTED ANSWERS: 3 TO 163

L5 3 SEA SSS SAM L4

=> s l4 full
FULL SEARCH INITIATED 13:28:17 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 74 TO ITERATE

100.0% PROCESSED 74 ITERATIONS 67 ANSWERS
SEARCH TIME: 00.00.01

L6 67 SEA SSS FUL L4

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 296.70 296.91

FILE 'CAPLUS' ENTERED AT 13:28:26 ON 09 OCT 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 9 Oct 2003 VOL 139 ISS 15

FILE LAST UPDATED: 8 Oct 2003 (20031008/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l6
L7 46 L6

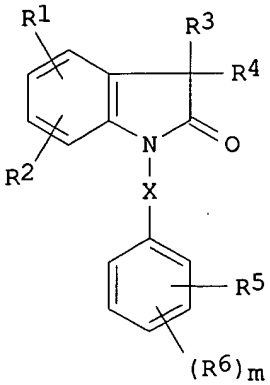
=> sort py
ENTER (L7), L#, OR L# RANGE:.
SORT ENTIRE ANSWER SET? (Y)/N:.
PROCESSING COMPLETED FOR L7
L8 46 SORT L7 PY

=> d 1-25 cbib pi abs hitstr

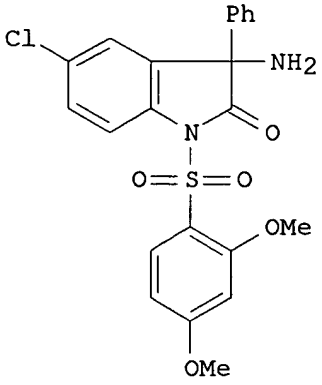
L8 ANSWER 1 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
1995:858609 Document No. 123:256516 Indol-2-one derivatives substituted in the 3-position by a nitrogenous group, their preparation, and pharmaceutical compositions containing them as vasopressin and/or oxytocin receptor ligands.. Wagnon, Jean; Tonnerre, Bernard; Di Malta, Alain; Roux, Richard; Amiel, Marie-Sophie; Serradeil-Legal, Claudine (Sanofi, Fr.). Fr. Demande FR 2714378 A1 19950630, 70 pp. (French). CODEN: FRXXBL. APPLICATION: FR 1993-15638 19931224.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2714378	A1	19950630	FR 1993-15638	19931224
	FR 2714378	B1	19960315		
	WO 9518105	A1	19950706	WO 1994-FR1528	19941223
	W: JP, LT, SI, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 687251	A1	19951220	EP 1995-905164	19941223
	EP 687251	B1	20020227		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08507092	T2	19960730	JP 1994-517812	19941223
	JP 3263081	B2	20020304	JP 1995-517812	19941223
	AT 213727	E	20020315	AT 1995-905164	19941223
	ES 2173172	T3	20021016	ES 1995-905164	19941223
	US 5594023	A	19970114	US 1995-500924	19950731
	US 5773612	A	19980630	US 1996-640080	19960430

GI



I



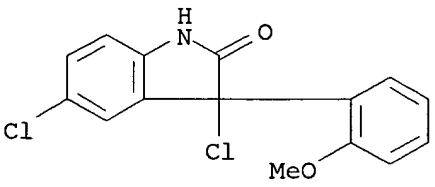
II

AB Title compds. I [R1, R2 = H, halo, alkyl, alkoxy, CF3; R3 = alkyl, cycloalkyl, (di)alkylcyclohexyl, (un)substituted Ph; R4 = N3, alkylsulfonamido, (un)substituted phenylsulfonamido, dimethylaminosulfonamido, (un)substituted NH2, heterocyclyl; R5 = H, R6; R6 = halo, alkyl, CF3, cyano, (di)(alkyl)aminomethyl, NO2, (un)substituted amino, carboxy, carbamoyl, acyl, etc.; X = SO2, CH2; m = 1, and sometimes 2-4] and salts are claimed, and approx. 100 examples are given. The compds. have affinity for vasopressin and/or oxytocin receptors, and are useful for treating disorders of the central and peripheral nervous, cardiovascular, renal, and gastric systems, as well as sexual disorders. For example, bromination of 5-chloro-1,3-dihydro-3-phenylindol-2-one with Br2 in CCl4 gave the 3-bromo derivative, which reaced with anhydrous NH3 in Et2O to give the 3-amino derivative Treatment of this with NaH in DMF and then with 2,4-(MeO)2C6H3SO2Cl yielded title compound II. In a test for inhibition of binding of [3H]-arginine-vasopressin to bovine renal V2 receptors, I had IC50 down to 10-9 M.

IT **169040-43-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of indolone derivs. as vasopressin and/or oxytocin receptor ligands)

RN 169040-43-1 CAPLUS

CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



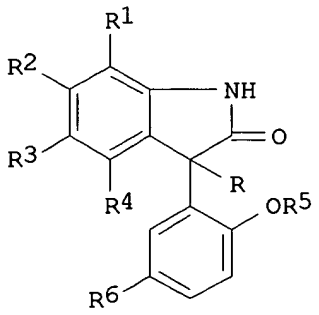
L8 ANSWER 2 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

1996:637685 Document No. 126:7989 Preparation of oxindole derivatives as potassium channel modulators. Hewawasam, Piyasena; Meanwell, Nicholas A.; Gribkoff, Valentin K. (Bristol-Myers Squibb Company, USA). U.S. US

5565483 A 19961015, 18 pp. (English). CODEN: USXXAM. APPLICATION: US 1995-477047 19950607.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5565483	A	19961015	US 1995-477047	19950607
	US 5602169	A	19970211	US 1996-635316	19960419
	CA 2176183	AA	19961208	CA 1996-2176183	19960509
	TW 384284	B	20000311	TW 1996-85105918	19960518
	IL 118349	A1	20000726	IL 1996-118349	19960521
	ZA 9604327	A	19971128	ZA 1996-4327	19960528
	NO 9602232	A	19961209	NO 1996-2232	19960531
	CZ 289248	B6	20011212	CZ 1996-1618	19960604
	EP 747354	A1	19961211	EP 1996-304188	19960606
	EP 747354	B1	20000816		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AU 9654757	A1	19961219	AU 1996-54757	19960606
	AU 707760	B2	19990722		
	AT 195515	E	20000915	AT 1996-304188	19960606
	ES 2148685	T3	20001016	ES 1996-304188	19960606
	RU 2165925	C2	20010427	RU 1996-111002	19960606
	JP 08333336	A2	19961217	JP 1996-145263	19960607
	CN 1144800	A	19970312	CN 1996-106834	19960607
	CN 1076348	B	20011219		
	SG 70572	A1	20000222	SG 1996-10008	19960607
	PL 184660	B1	20021129	PL 1996-314672	19960607
	HK 1003301	A1	20010427	HK 1998-102434	19980323

GI



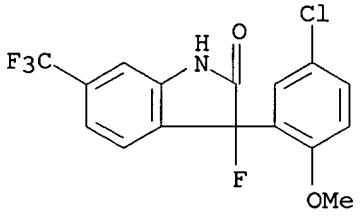
I

AB The title compds. I [R is hydrogen, hydroxy or fluoro; R1, R2, R3 and R4 each are independently hydrogen, alkyl, halogen, trifluoromethyl, Ph, p-methylphenyl or p-trifluoromethylphenyl; or R1 and R2 , R2 and R3 or R3 and R4 are joined together to form a benzo fused ring; R5 is hydrogen or alkyl; and R6 is chlorine or trifluoromethyl], useful as openers of the large-conductance calcium-activated potassium channels, are prepared In a test using Xenopus oocytes, (±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one (preparation given) at 20 μM increased the BK current by > 150%.

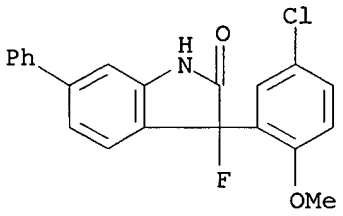
IT **183720-28-7P 183720-32-3P 183720-33-4P**
183720-35-6P 183720-37-8P 183720-38-9P
183720-39-0P 183720-40-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of oxindole derivs. as potassium channel modulators)

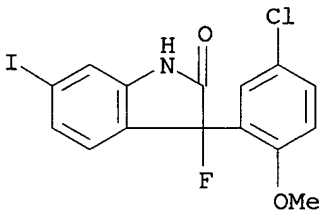
RN 183720-28-7 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



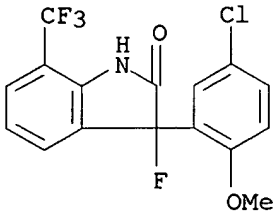
RN 183720-32-3 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-phenyl- (9CI) (CA INDEX NAME)



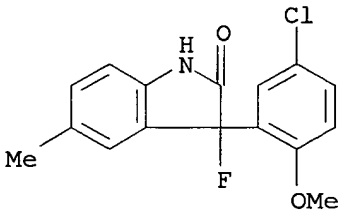
RN 183720-33-4 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-iodo- (9CI) (CA INDEX NAME)



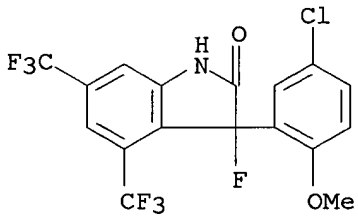
RN 183720-35-6 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-7-(trifluoromethyl)- (9CI) (CA INDEX NAME)



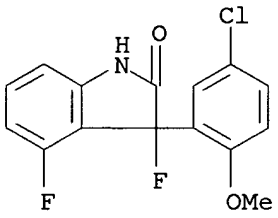
RN 183720-37-8 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-5-methyl- (9CI) (CA INDEX NAME)



RN 183720-38-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-4,6-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)

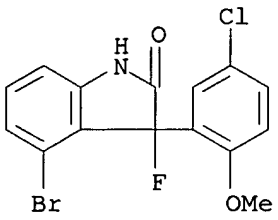


RN 183720-39-0 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3,4-difluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 183720-40-3 CAPLUS
CN 2H-Indol-2-one, 4-bromo-3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-

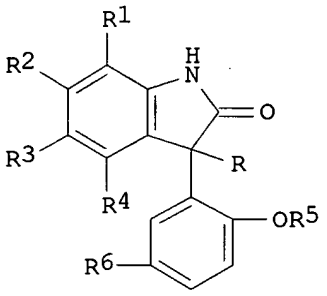
(9CI) (CA INDEX NAME)



L8 ANSWER 3 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
1997:128099 Document No. 126:181369 3-substituted oxindole derivatives as potassium channel modulators, and preparation and therapeutic use thereof. Hewawasam, Piyasena; Meanwell, Nicholas A.; Gribkoff, Valentin K. (Bristol-Myers Squibb Company, USA). U.S. US 5602169 A 19970211, 17 pp., Cont.-in-part of U.S. Ser. No. 477, 047. (English). CODEN: USXXAM. APPLICATION: US 1996-635316 19960419. PRIORITY: US 1995-477047 19950607.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US-5602169	A	19970211	US 1996-635316	19960419
US-5565483	A	19961015	US 1995-477047	19950607

GI



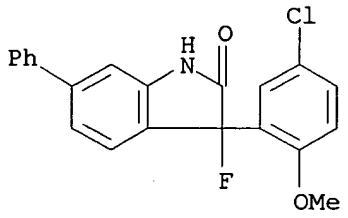
I

AB Substituted 3-Ph oxindole derivs. I(R = H, OH, F; R1-R4 = H, C1-4 alkyl, halo, CF3, Ph, p-methylphenyl, p-trifluoromethylphenyl; or R1 and R2, R2 and R3 or R3 and R4 are joined together to form a benzo fused ring; R5= H, C1-4 alkyl; R6 = Cl, CF3) and nontoxic pharmaceutically acceptable salts, solvates, or hydrates thereof, are provided which are openers of the large-conductance calcium-activated potassium channels and are useful in the treatment of disorders which are responsive to the opening of the potassium channels. Preparation of e.g. (±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indole-2-one is described. Compds. of the invention can be used in the treatment of e.g. ischemia, asthma, or traumatic brain injury.

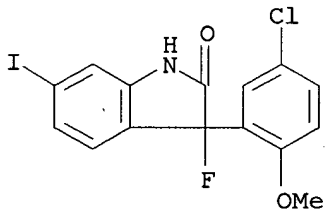
IT **183720-32-3P 183720-33-4P 183720-35-6P 183720-37-8P 183720-38-9P 187523-35-9P 187523-36-0P 187523-40-6P 187523-41-7P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oxindole derivative preparation for potassium channel modulators, and therapeutic use thereof)

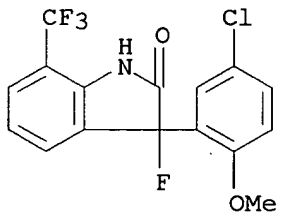
RN 183720-32-3 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-phenyl- (9CI) (CA INDEX NAME)



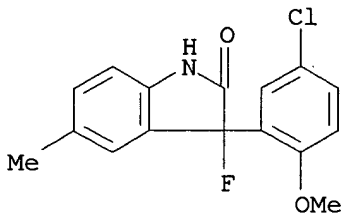
RN 183720-33-4 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-iodo- (9CI) (CA INDEX NAME)



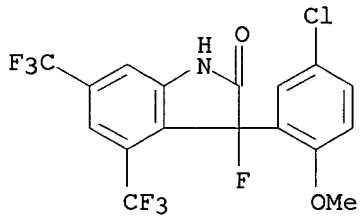
RN 183720-35-6 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-7-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 183720-37-8 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-5-methyl- (9CI) (CA INDEX NAME)

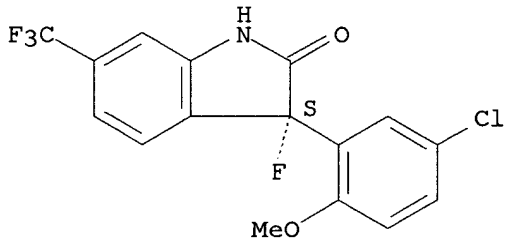


RN 183720-38-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-4,6-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)



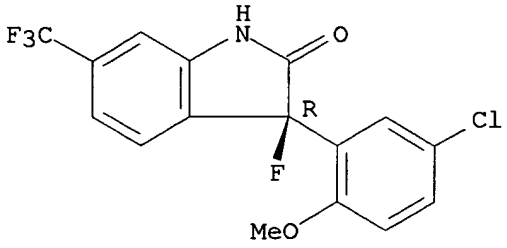
RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

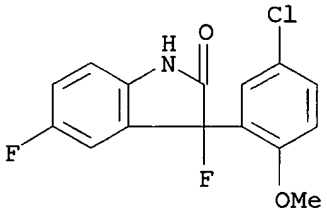


RN 187523-36-0 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3R)- (9CI) (CA INDEX NAME)

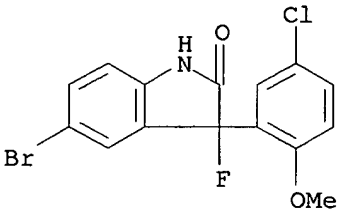
Absolute stereochemistry. Rotation (-).



RN 187523-40-6 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3,5-difluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



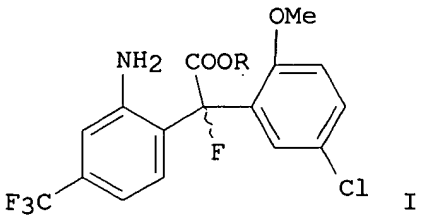
RN 187523-41-7 CAPLUS
CN 2H-Indol-2-one, 5-bromo-3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



L8 ANSWER 4 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
1998:604716 Document No. 129:230636 Preparation of 3-fluorooxindole derivatives. Pendri, Yadagiri R.; Martinez, Eduardo J.; Thottathil, John K.; Hewawasam, Piyasena (Bristol-Myers Squibb Company, USA). U.S. US 5808095 A 19980915, 9 pp. (English). CODEN: USXXAM. APPLICATION: US 1997-946393 19971007.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5808095	A	19980915	US 1997-946393	19971007
	US 5892106	A	19990406	US 1998-99472	19980618

GI



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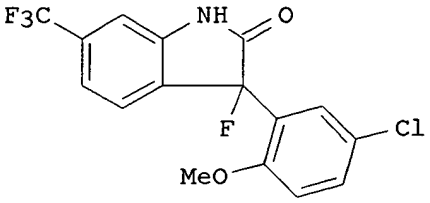
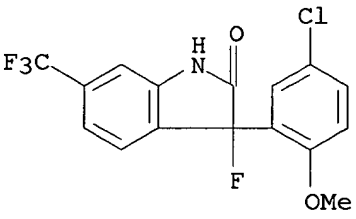


II

AB The present invention relates to novel intermediates [I; the wavy bond represents the racemate, the (R)-enantiomer or the (S)-enantiomer; and R is hydrogen, a carboxyl-protecting group or a cation of an addition salt]. The process for the preparation of certain 3-fluoro oxindole derivs. by reduction and cyclization is also claimed. Thus, I (R = Me) (preparation given) was treated with Bu4NCl, Na2S2O4, and HCl to give 73% compound (II).

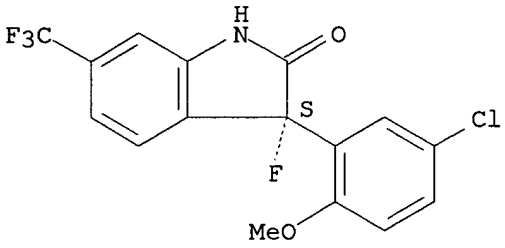
IT **183720-28-7P 187523-35-9P 187523-36-0P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 3-fluorooxindole derivs.)

RN 183720-28-7 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



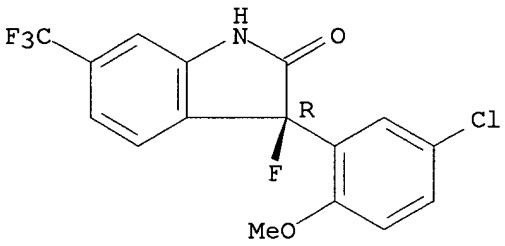
RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 187523-36-0 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

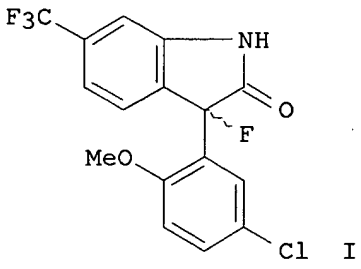


L8 ANSWER 5 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
1998:251051 Document No. 128:294696 Process for preparing racemic 3-fluorooxindole derivatives and their resolution. Pendri, Yadagiri R.; Martinez, Eduardo J.; Thottathil, John K.; Hewawasam, Piyasena (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 9816222 A1 19980423, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 1997-US15323 19971007. PRIORITY: US 1996-28296 19961011; US 1996-27543 19961015; US 1997-48218 19970530.

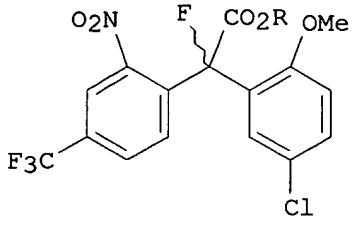
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9816222	A1	19980423	WO 1997-US15323	19971007
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	TW 457233	B	20011001	TW 1997-86114472	19971003
	AU 9747343	A1	19980511	AU 1997-47343	19971007
	AU 728455	B2	20010111		

EP 946173 A1 19991006 EP 1997-909835 19971007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 2001524935 T2 20011204 JP 1998-518325 19971007
KR 2000049067 A 20000725 KR 1999-703140 19990410

GI



I

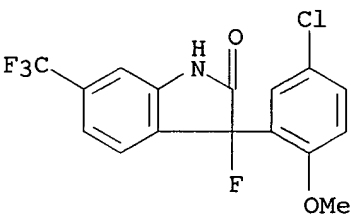


II

AB The title compds. [I; wavy bond = racemate, (R)- or (S)-enantiomer], useful as intermediates for the preparation of modulators of the large-conductance Ca-activated K (maxi-K) channels, were prepared by reducing compds. II (R = H, carboxy-protecting group, cation; wavy bond as above) or their solvates to their amino analogs, and cyclization. The compds. II, a process for resolving racemates II (R = H) (III) and a process for preparing racemates III by fluorination of their benzylic H-containing precursors with N-fluorobis(phenylsulfonyl)amine are also claimed. Thus, the racemic 5-chloro-α-fluoro-2-methoxy-α-[2-nitro-4-(trifluoromethyl)phenyl]benzeneacetic acid Me ester (3-step preparation given) was saponified and the free acid resolved by selective crystallization of its salts with (S)- and (R)-α-methylbenzylamine.

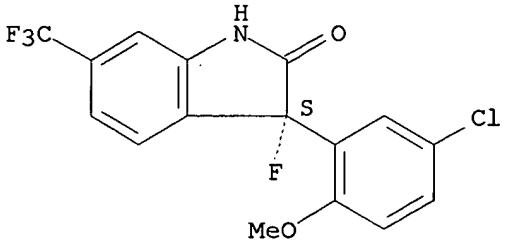
IT **183720-28-7P 187523-35-9P 187523-36-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing racemic 3-fluorooxindole derivs. and their resolution)

RN 183720-28-7 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



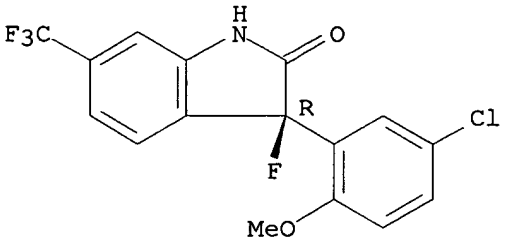
RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 187523-36-0 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

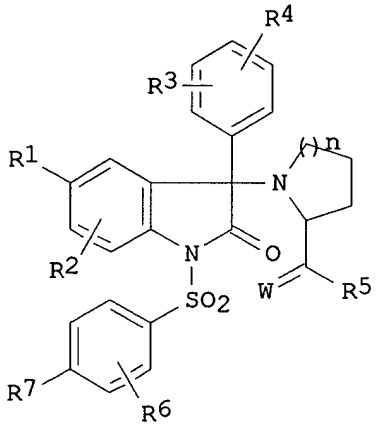


L8 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:935598 Document No. 136:69734 Preparation and use of dihydroindolone derivatives as vasopressin receptor ligands. Roux, Richard; Serradeil-Le Gal, Claudine; Wagnon, Jean (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2001098295 A1 20011227, 91 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2001-FR1919 20010619. PRIORITY: FR 2000-7885 20000619.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001098295	A1	20011227	WO 2001-FR1919	20010619
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	FR 2810320	A1	20011221	FR 2000-7885	20000619

FR 2810320 B1 20020823
EP 1296976 A1 20030402 EP 2001-947534 20010619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2003162767 A1 20030828 US 2002-311435 20021216

GI



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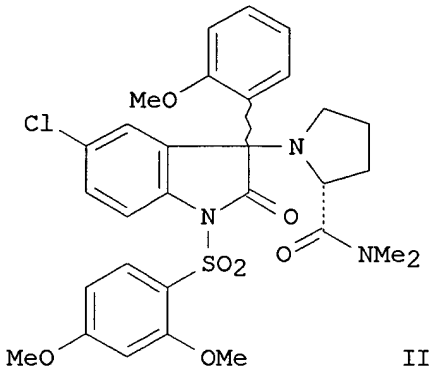


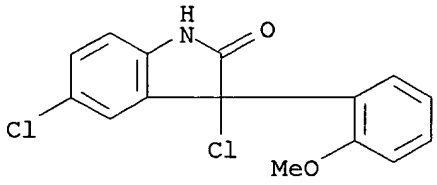
II

AB Title compds. I [W = O, S; R1 = halo, alkyl, alkoxy, CF3(O); R2 = H, halo, alkyl, alkoxy, CF3 or R2 is in the 6-position of the indol-2-one nucleus and forms a trimethylene bridge with R1; R3 halo, OH, alkyl, alkoxy, CF3O; R4 = H, halo, alkyl, alkoxy, or R3, R4 form a methylenedioxy bridge in the 2,3 position of the Ph ring; R5 = EtNH, NMe2, azetidin-1-yl, alkoxy; R6 = alkoxy; R7 = alkoxy] were prepared Over 35 synthetic examples were disclosed. E.g., addition 2-Methoxyphenylmagnesium bromide to 5-chloro-1H-indol-2,3-dione in ether followed by treatment of the resulting carbinol with thionyl chloride provided the corresponding α-chloro-indol-2-one derivative This was reacted with 2(S)-N,N-dimethylcarboxamidopyrrolidine (CHCl3, THF, i-Pr2NEt) and the resulting indole sulfonylated with 2,4-dimethoxysulfonyl chloride (DMF, NaH) which yielded II. I exhibit affinity and selectivity for V1b arginine-vasopressin receptors or for both V1b and V1a arginine-vasopressin receptors.

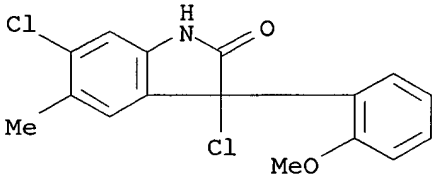
IT **169040-43-1P**, 3,5-Dichloro-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one **352030-16-1P**, 3,6-Dichloro-3-(2-methoxyphenyl)-5-methyl-1,3-dihydro-2H-indol-2-one **352277-91-9P**, 3,5-Dichloro-3-(2,3-dimethoxyphenyl)-1,3-dihydro-2H-indol-2-one **352278-10-5P 352278-14-9P**, 3,5-Dichloro-3-(2-trifluoromethoxyphenyl)-1,3-dihydro-2H-indol-2-one **352278-48-9P**, 3,5,6-Trichloro-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one **358627-02-8P**, 3,5-Dichloro-3-(2,4-dimethoxyphenyl)-1,3-dihydro-2H-indol-2-one **358627-08-4P**, 3,4-Dichloro-3-(2-methoxyphenyl)-5-methyl-1,3-dihydro-2H-indol-2-one **365525-99-1P 383424-82-6P 383424-88-2P**, 3,5-Dichloro-3-(2-benzyloxyphenyl)-1,3-dihydro-2H-indol-2-one **383424-90-6P**, 3,5-Dichloro-3-(2-methoxy-6-methylphenyl)-1,3-dihydro-2H-indol-2-one **383424-92-8P**, 3-Chloro-3-(2-methoxyphenyl)-5-trifluoromethoxy-1,3-dihydro-2H-indol-2-one **383425-03-4P**, 3-Chloro-3-(2-methoxy-6-methylphenyl)-5,6-dimethyl-1,3-dihydro-2H-indol-2-one **383425-05-6P**, 3,5-Dichloro-3-(2-methoxyphenyl)-6-trifluoromethyl-1,3-dihydro-2H-indol-

2-one
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation and use of dihydroindolone derivs. as vasopressin receptor ligands)

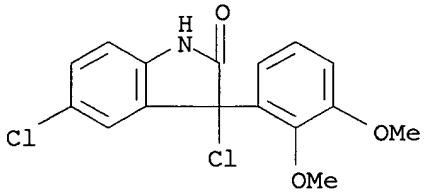
RN 169040-43-1 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



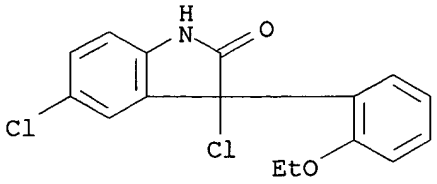
RN 352030-16-1 CAPLUS
CN 2H-Indol-2-one, 3,6-dichloro-1,3-dihydro-3-(2-methoxyphenyl)-5-methyl- (9CI) (CA INDEX NAME)



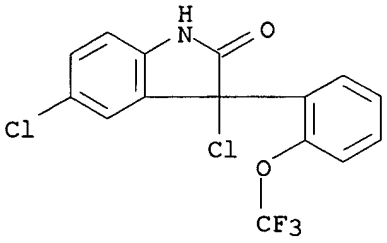
RN 352277-91-9 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2,3-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



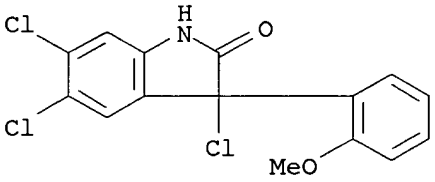
RN 352278-10-5 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2-ethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



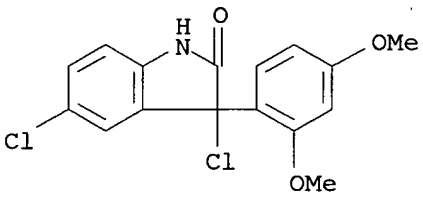
RN 352278-14-9 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-[2-(trifluoromethoxy)phenyl]- (9CI) (CA INDEX NAME)



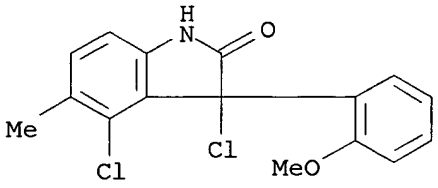
RN 352278-48-9 CAPLUS
CN 2H-Indol-2-one, 3,5,6-trichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 358627-02-8 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2,4-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)

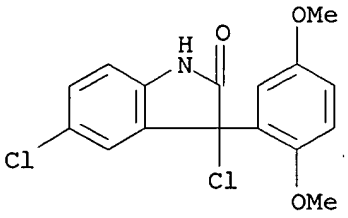


RN 358627-08-4 CAPLUS
CN 2H-Indol-2-one, 3,4-dichloro-1,3-dihydro-3-(2-methoxyphenyl)-5-methyl- (9CI) (CA INDEX NAME)

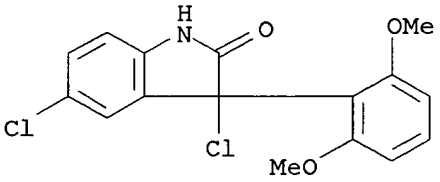


RN 365525-99-1 CAPLUS

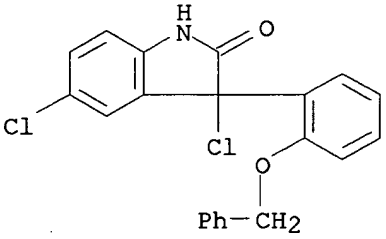
CN 2H-Indol-2-one, 3,5-dichloro-3-(2,5-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



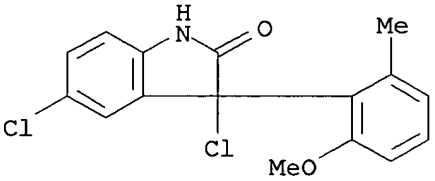
RN 383424-82-6 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2,6-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 383424-88-2 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-[2-(phenylmethoxy)phenyl]- (9CI) (CA INDEX NAME)

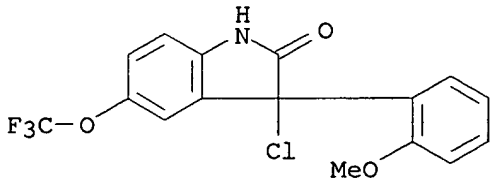


RN 383424-90-6 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxy-6-methylphenyl)- (9CI) (CA INDEX NAME)

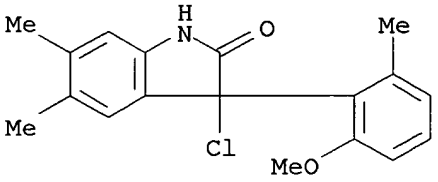


RN 383424-92-8 CAPLUS
CN 2H-Indol-2-one, 3-chloro-1,3-dihydro-3-(2-methoxyphenyl)-5-

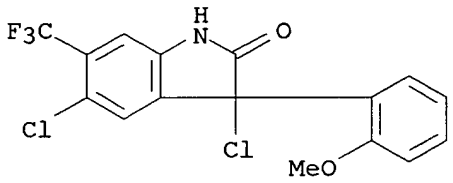
(trifluoromethoxy)- (9CI) (CA INDEX NAME)



RN 383425-03-4 CAPLUS
CN 2H-Indol-2-one, 3-chloro-1,3-dihydro-3-(2-methoxy-6-methylphenyl)-5,6-dimethyl- (9CI) (CA INDEX NAME)



RN 383425-05-6 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 7 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:887503 Document No. 136:193602 In vitro protein binding studies with BMS-204352: lack of protein binding displacement interaction in human serum. Krishna, Rajesh; Yao, Ming; Kaczor, Donna; Vachharajani, Nimish; Srinivas, Nuggehally R. (Clinical Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, USA). Biopharmaceutics & Drug Disposition, 22(1), 41-44 (English) 2001. CODEN: BDDID8. ISSN: 0142-2782. Publisher: John Wiley & Sons Ltd..
AB BMS-204352, a maxi-K channel opener, is currently under development for the treatment of stroke. Protein binding of BMS-204352 was determined in sera from several species, namely, rat, monkey, dog, and human. Data indicated that the compound was shown to be highly protein bound in serum from all species (99.6%). In order to test for the potential for drug-drug interactions and competitive displacement of BMS-204352 by diazepam, phenytoin, propranolol, and warfarin, in vitro expts. were performed using spiked human serum and ex vivo human plasma samples. Protein binding was determined using equilibrium dialysis for 4 h at maximal therapeutic concns. for each drug alone or in appropriate combination in spiked serum samples. Ex vivo samples from a clin. BMS-204352 study (0, 1, and 24 h) were dialyzed

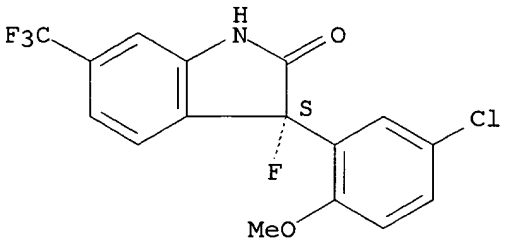
sep. after addition of diazepam, phenytoin, propranolol, or warfarin. Drug content in biol. matrixes was measured for radioactivity using liquid scintillation counting. Results indicated that (1) addition of diazepam, phenytoin, propranolol, or warfarin did not alter the free fraction of BMS-204352; (2) BMS-204352 did not displace diazepam, phenytoin, propranolol, or warfarin from their protein binding sites, and (3) comparison of ex vivo plasma samples after BMS-204352 dosing indicated no impact of BMS-204352 and/or its metabolites on the free fraction of diazepam, phenytoin, propranolol, or warfarin. In conclusion, the potential for a drug-drug interaction due to alterations in protein binding with BMS-204352 is unlikely.

IT **187523-35-9**, BMS-204352
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(in vitro protein binding studies with BMS-204352 and lack of protein binding displacement drug interactions in human serum)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 8 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2001:747752 Document No. 135:303770 Preparation of indolin-2-one derivatives and their use as oxytocin receptor ligands. Foulon, Loiec; Garcia, Georges; Serradeil-le Gal, Claudine; Valette, Gerard (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2001074775 A1 20011011, 122 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2001-FR980 20010402. PRIORITY: FR 2000-4193 20000403.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001074775	A1	20011011	WO 2001-FR980	20010402

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2807038	A1	20011005	FR 2000-4193	20000403
FR 2807038	B1	20020816		
EP 1272468	A1	20030108	EP 2001-919610	20010402
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001009814	A	20030121	BR 2001-9814	20010402
NZ 521617	A	20030530	NZ 2001-521617	20010402
JP 2003529586	T2	20031007	JP 2001-572470	20010402
NO 2002004749	A	20021203	NO 2002-4749	20021002

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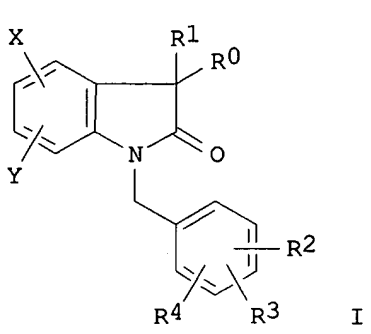

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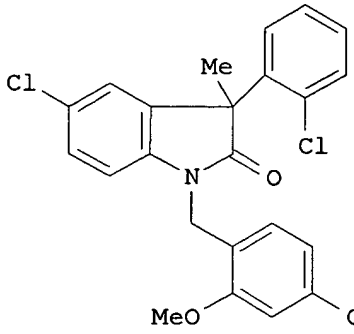


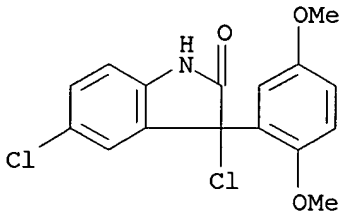
II

AB Title compds. I [R0 = substituted Ph, pyridyl; R1 = alk(en/yn)yl, alkoxycarbonyl, phenyloxycarbonyl, etc.; R2, R4 = H, Cl, F, alkyl, alkoxy; R3 = Cl, F, alkyl, alkoxy, OH, carbamoyl, alkylcarbonylamino, NO2, CN, etc.; X, Y = H, Cl, Br, I, F, alkoxy, CF3] were prepared Over 200 examples were prepared E.g., 5-chloro-3-(2-chlorophenyl)-3-methylindolin-2-one (preparation given) was treated with t-BuOK in THF @ -40°C, warmed to 0°C and cooled to -60°C. To this cooled mixture was added a solution of 2,4-dimethoxyphenylmethanol that was reacted with PBr3 (Et2O, -50°C - 0°C); the resulting solution warmed to room temperature to give II after work-up. Enantiomers of II were obtained by chiral chromatog. I have affinity for oxytocin receptors (no data) and are used to treat (e.g.) autism, depression, schizophrenia, etc.

IT **365525-99-1P**, 3,5-Dichloro-3-(2,5-dimethoxyphenyl)indolin-2-one
365526-44-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of indolin-2-one derivs. and their use as oxytocin receptor ligands)

RN 365525-99-1 CAPLUS

CN 2H-Indol-2-one, 3,5-dichloro-3-(2,5-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 365526-44-9 CAPLUS
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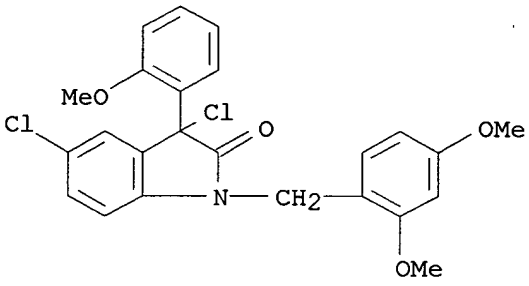


L8 ANSWER 9 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:716099 Document No. 136:395791 The maxi-K channel opener BMS-204352 attenuates regional cerebral edema and neurologic motor impairment after experimental brain injury. Cheney, Jessica A.; Weisser, Justin D.; Bareyre, Florence M.; Laurer, Helmut L.; Saatman, Kathryn E.; Raghupathi, Ramesh; Gribkoff, Valentin; Starrett, John E., Jr.; McIntosh, Tracy K. (Department of Neurosurgery, School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA). Journal of Cerebral Blood Flow and Metabolism, 21(4), 396-403 (English) 2001. CODEN: JCBMDN. ISSN: 0271-678X. Publisher: Lippincott Williams & Wilkins.

AB Large-conductance, calcium-activated potassium (maxi-K) channels regulate neurotransmitter release and neuronal excitability, and openers of these channels have been shown to be neuroprotective in models of cerebral ischemia. This work evaluated the effects of postinjury systemic administration of the maxi-K channel opener BMS-204352 on behavioral and histol. outcome after lateral fluid percussion traumatic brain injury in the rat. Anesthetized Sprague-Dawley rats were subjected to moderate fluid percussion brain injury or surgery without injury and were randomized to receive a bolus of 0.1 or 0.03 mg BMS-204352/kg or vehicle 10 min postinjury. One group of rats was tested for memory retention (Morris water maze) 42 h postinjury, and then were killed for evaluation of regional cerebral edema. A 2nd group of injured/sham rats was assessed for neurol. motor function from 48 h to 2 wk postinjury, and for cortical lesion area. Administration of 0.1 mg BMS-204352/kg improved neurol. motor function 1 and 2 wk postinjury and reduced the extent of cerebral edema in the ipsilateral hippocampus, thalamus, and adjacent cortex. Administration of 0.03 mg BMS-204352/kg reduced cerebral edema in the ipsilateral thalamus. No effects on cognitive function or cortical tissue loss were observed with either dose. The novel maxi-K channel opener

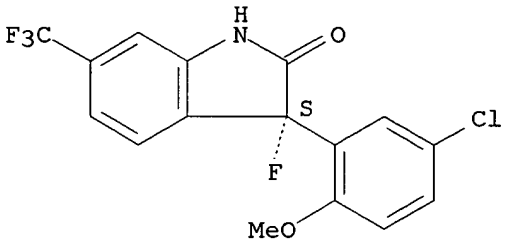
BMS-204352 may be selectively beneficial in the treatment of exptl. traumatic brain injury.

IT **187523-35-9**, BMS 204352
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(maxi-potassium channel opener BMS-204352 attenuation of regional cerebral edema and neurol. motor impairment after brain injury)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 10 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2001:661414 Document No. 135:210939 Novel 1,3-dihydro-2H-indol-2-ones, preparation, pharmaceutical compositions containing same and use for treating pathologies involving arginine-vasopressin receptors. Serradeil-le Gal, Claudine; Tonnerre, Bernard; Wagnon, Jean (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2001064668 A2 20010907, 56 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2001-FR509 20010222. PRIORITY: FR 2000-2488 20000225.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001064668	A2	20010907	WO 2001-FR509	20010222
	WO 2001064668	A3	20020314		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	FR 2805536	A1	20010831	FR 2000-2488	20000225
	FR 2805536	B1	20020823		
	EP 1259505	A2	20021127	EP 2001-907866	20010222
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

JP 2003525287	T2	20030826	JP 2001-563508	20010222
US 2003109545	A1	20030612	US 2002-203730	20020812
US 6596732	B2	20030722		

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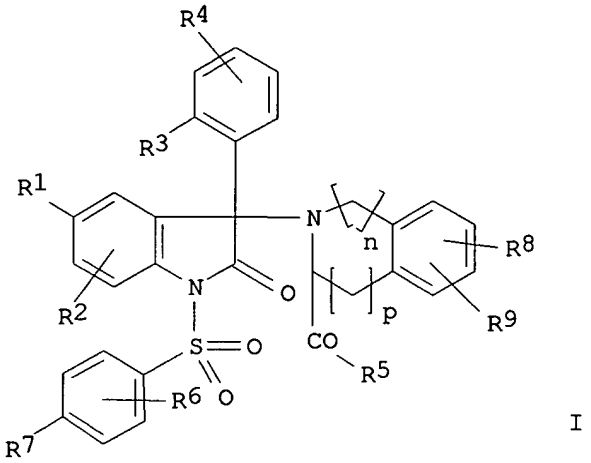


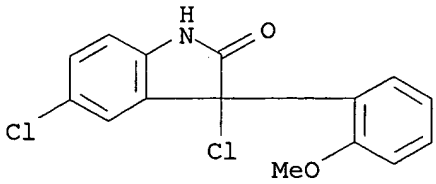
I

AB The invention concerns compds. (I; e.g. levorotatory isomer of (1S)-2-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-N,N-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide) and their solvates and/or hydrates, having affinity and selectivity for V1b or for both V1b and V1a arginine-vasopressin receptors (no data). The invention also concerns a method for preparing them, intermediate compds. (II = I with H in place of the phenylsulfonyl) useful for preparing them, pharmaceutical compns. containing them, and their use for preparing medicines. In I: n = 0-2; p= 0-2; n + p = 1, 2; R1 = halogen, (C1-C4)alkyl, (C1-C4)alkoxy, trifluoromethyl, trifluoromethoxy; R2 = H; halogen, (C1-C4)alkyl, (C1-C4)alkoxy, trifluoromethyl; or R2 is in position 6 of the indol-2-one ring and R1 and R2 together = trimethylene; R3 = halogen, hydroxy, (C1-C2)alkyl, (C1-C2)alkoxy, trifluoromethoxy; R4 = H, halogen, (C1-C2)alkyl, (C1-C2)alkoxy; or R4 is in position 3 of the Ph and R3 and R4 together = methylenedioxy; R5 = ethylamino, dimethylamino, azetidin-1-yl, (C1-C2)alkoxy; R6 = (C1-C4)alkoxy; R7 = (C1-C4)alkoxy; R8 = H, halogen, (C1-C4)alkyl, (C1-C4)alkoxy; R9 = H, halogen, (C1-C4)alkyl, (C1-C4)alkoxy. I are prepared from II and R6-4-R7C6H3SO2Hal (Hal = halogen) in the presence of base.

IT **169040-43-1P**, 3,5-Dichloro-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one **352030-16-1P**, 3,6-Dichloro-3-(2-methoxyphenyl)-5-methyl-1,3-dihydro-2H-indol-2-one **352030-19-4P**, 3,5-Dichloro-3-(2-methoxyphenyl)-6-methyl-1,3-dihydro-2H-indol-2-one **352277-91-9P**, 3,5-Dichloro-3-(2,3-dimethoxyphenyl)-1,3-dihydro-2H-indol-2-one **352278-48-9P**, 3,5,6-Trichloro-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one **358627-02-8P 358627-08-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of indolones useful for treating pathologies involving arginine-vasopressin receptors)

RN 169040-43-1 CAPLUS

CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 352030-16-1 CAPLUS
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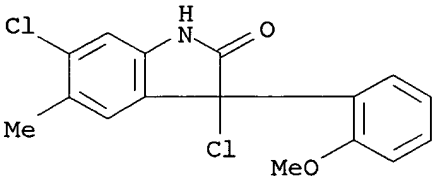

RN 352030-19-4 CAPLUS
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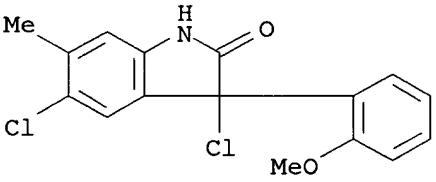
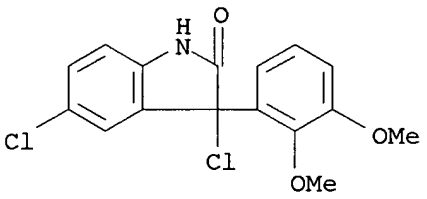
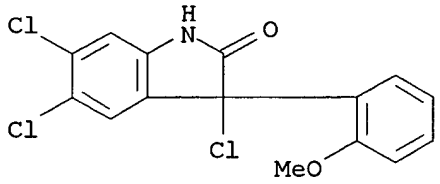


RN 352277-91-9 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2,3-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 352278-48-9 CAPLUS
CN 2H-Indol-2-one, 3,5,6-trichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 358627-02-8 CAPLUS
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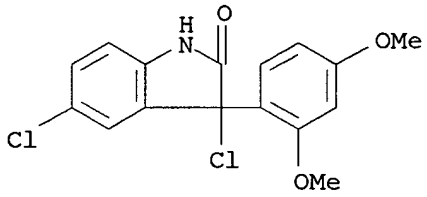
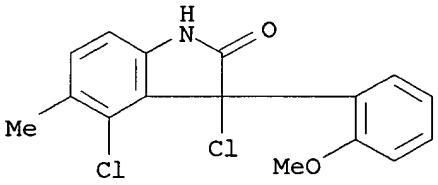


RN 358627-08-4 CAPLUS
CN 2H-Indol-2-one, 3,4-dichloro-1,3-dihydro-3-(2-methoxyphenyl)-5-methyl- (9CI) (CA INDEX NAME)



L8 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:565027 Document No. 135:137403 Preparation of 1,3-dihydro-2H-indol-2-ones with selective binding affinity for the V1b arginine-vasopressin receptor for pharmaceutical use. Schoentjes, Bruno; Serradeil-Le Gal, Claudine; Wagnon, Jean (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2001055134 A2 20010802, 34 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (French). CODEN: PIXXD2.
APPLICATION: WO 2001-FR228 20010124. PRIORITY: FR 2000-958 20000125.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001055134	A2	20010802	WO 2001-FR228	20010124
	WO 2001055134	A3	20020314		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,

HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2804115	A1	20010727	FR 2000-958	20000125
FR 2804115	B1	20020308		
EP 1254134	A2	20021106	EP 2001-907687	20010124
EP 1254134	B1	20030723		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003523354	T2	20030805	JP 2001-560993	20010124
AT 245644	E	20030815	AT 2001-1907687	20010124
US 2003139413	A1	20030724	US 2002-182638	20021125
US 6624164	B2	20030923		

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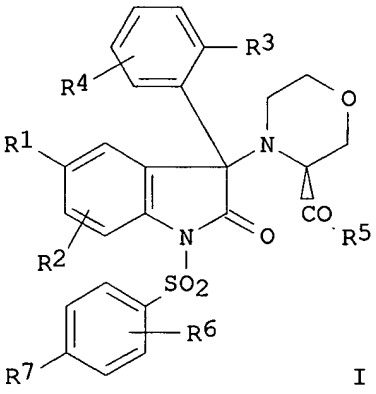

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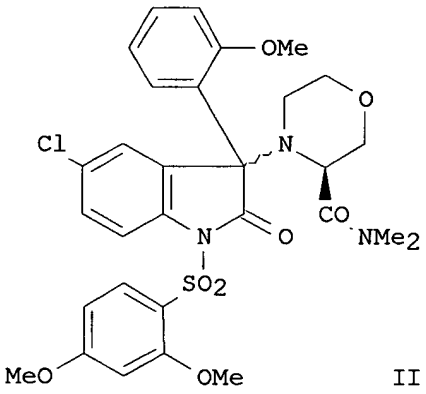
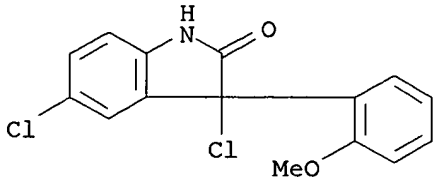


II

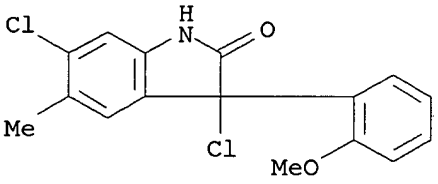
AB Morpholinylindolines, such as I [R1 = CF3, OCF3, halogen, alkyl, alkoxy; R2 = H, CF3, halogen, alkyl, alkoxy; R3 = OH, OCF3, halogen, alkyl, alkoxy; R4 = H, halogen, alkyl, alkoxy; R3R4 = OCH2O; R5 = NHEt, NMe2, azetidin-1-yl, alkoxy; R6, R7 = alkoxy] having affinity and selectivity for V1b receptors or for both V1b and V1a arginine-vasopressin receptors, were prepared for pharmaceutical use in the treatment of a variety of conditions, such as hypertension, migraine, myocardial infarction, pulmonary hypertension, etc. Thus, both diastereomers of morpholinylindolinone II were prepared via a multistep synthetic sequence starting from 1-bromo-2-methoxybenzene, 5-chloro-1H-indole-2,3-dione, L-serine, and 2,4-dimethoxybenzenesulfonyl chloride. Binding affinity of the prepared morpholinylindolines for V1b and V1a arginine-vasopressin receptors was tested with the V1b receptor being selectively inhibited.

IT **169040-43-1P 352030-16-1P 352030-19-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 1,3-dihydro-2H-indol-2-ones with selective binding affinity for the V1b arginine-vasopressin receptor for pharmaceutical use treating conditions such as hypertension)

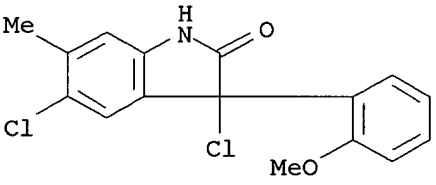
RN 169040-43-1 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 352030-16-1 CAPLUS
CN 2H-Indol-2-one, 3,6-dichloro-1,3-dihydro-3-(2-methoxyphenyl)-5-methyl- (9CI) (CA INDEX NAME)



RN 352030-19-4 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)-6-methyl- (9CI) (CA INDEX NAME)



L8 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:565024 Document No. 135:152717 Preparation of N-oxoindolylpyrrolidine-2-carboxamides and analogs as vasopressin V1a and V1b receptor ligands. Roux, Richard; Serradeil-Le Gal, Claudine; Tonnerre, Bernard; Wagnon, Jean (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2001055130 A2 20010802, 82 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2001-FR226 20010124. PRIORITY: FR 2000-957 20000125.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001055130	A2	20010802	WO 2001-FR226	20010124
	WO 2001055130	A3	20020314		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2804114	A1	20010727	FR 2000-957	20000125
FR 2804114	B1	20020308		
BR 2001007807	A	20021022	BR 2001-7807	20010124
EP 1255751	A2	20021113	EP 2001-907685	20010124
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003523351	T2	20030805	JP 2001-560989	20010124
NO 2002003510	A	20020925	NO 2002-3510	20020723
BG 106947	A	20030430	BG 2002-106947	20020723
US 2003114683	A1	20030619	US 2002-182048	20020724

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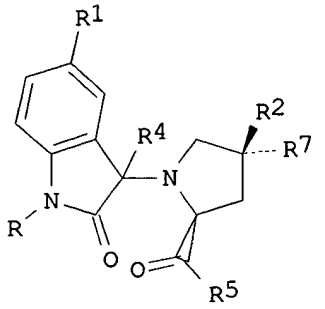


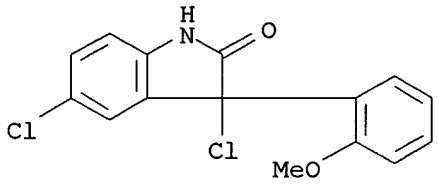
I

AB Title compds. [(un)substituted I; R = 2,4- or 3,4-dialkoxyphenylsulfonyl; R1 = halo, alkyl, alkoxy, CF3, OCF3; 1 of R2,R7 = OR6 and the other = H; R4 = ZR3; R3 = halo, OH, alkyl, alkoxy, OCF3; R5 = NHEt, NMe2, azetidino, alkoxy; R7 = H, alkyl, alkoxycarbonylalkyl, etc.; Z = (un)substituted 1,2-phenylene] were prepared Thus, 5-chloroindole-2,3-dione was condensed with 2-(MeO)C6H4MgBr and the chlorinated product aminated by (2S,4R)-4-hydroxy-N,N-dimethyl-2-pyrrolidinecarboxamide (preparation given) to give (+)- and (-)-I [R1 = Cl, R2 = H, R4 = C6H4(OMe)-2, R5 = NMe2, R7 = OH][(+)- and (-)-II; R = H] the latter of which was condensed with 2,4-(MeO)2C6H3SO2Cl to give (-)-II [R = SO2C6H3(OMe)2-2,4]. Data for biol. activity of I were given.

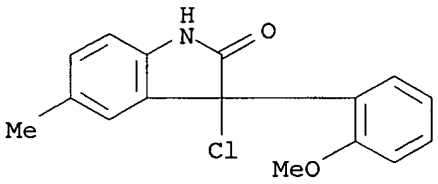
IT **169040-43-1P 352277-69-1P 352277-91-9P 352278-10-5P 352278-14-9P 352278-48-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-oxoindolylpyrrolidine-2-carboxamides and analogs as vasopressin V1a and V1b receptor ligands)

RN 169040-43-1 CAPLUS

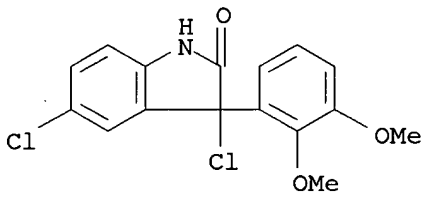
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



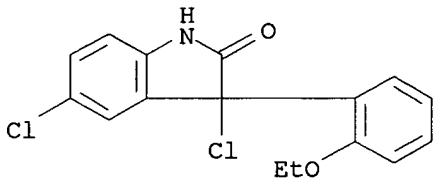
RN 352277-69-1 CAPLUS
CN 2H-Indol-2-one, 3-chloro-1,3-dihydro-3-(2-methoxyphenyl)-5-methyl- (9CI) (CA INDEX NAME)



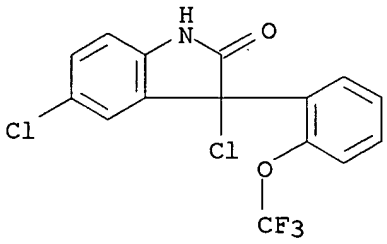
RN 352277-91-9 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2,3-dimethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



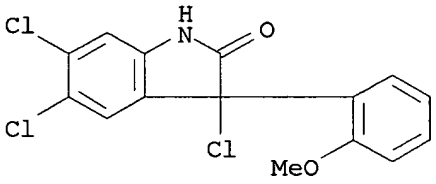
RN 352278-10-5 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-3-(2-ethoxyphenyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



RN 352278-14-9 CAPLUS
CN 2H-Indol-2-one, 3,5-dichloro-1,3-dihydro-3-[2-(trifluoromethoxy)phenyl]- (9CI) (CA INDEX NAME)

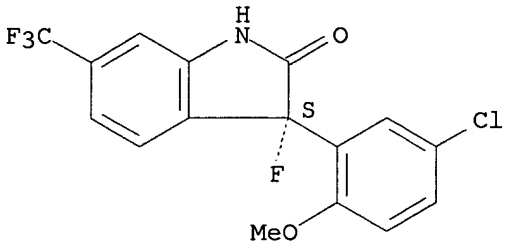


RN 352278-48-9 CAPLUS
CN 2H-Indol-2-one, 3,5,6-trichloro-1,3-dihydro-3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 13 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:536151 Document No. 135:312971 BMS-204352(Bristol-Myers Squibb). Mackay, Kenneth B. (Department of Neuroscience, Neurocrine Biosciences Inc, San Diego, CA, 92121-1102, USA). Current Opinion in Investigational Drugs (PharmaPress Ltd.), 2(6), 820-823 (English) 2001. CODEN: COIDAZ. Publisher: PharmaPress Ltd..
AB A review with refs. BMS-204352 is a fluoro-oxindole potassium channel opener being developed by Bristol-Myers Squibb as a potential neuroprotectant for the treatment of acute ischemic stroke. Phase I trials were underway in Japan in 1998. By July 1999, it was in phase II trials in the US and by Oct. 2000, phase II trials had also begun in Japan. At the 219th American Chemical Society meeting in Mar. 2000, it was reported that BMS-204352 had entered worldwide phase III trials involving patients with suspected acute stroke. In Feb. 2001, Credit Suisse First Boston predicted sales of $111 million in 2005. In Feb. 1999, Lehman Brothers predicted the drug had a 30% probability of reaching market, with an estimated first launch date in 2004. The analysts predicted peak sales would occur in 2008, with sales of $500 million in the US at that time.
IT **187523-35-9**, BMS-204352
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMS-204352 as a potential neuroprotectant for treatment of acute ischemic stroke)
RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



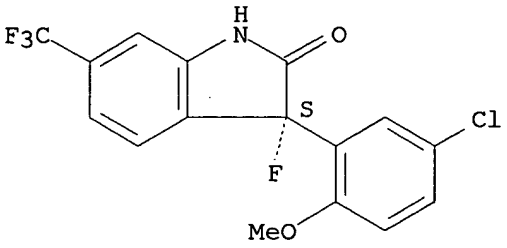
L8 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:389379 Document No. 135:221181 KCNQ4 channel activation by BMS-204352 and retigabine. Schroder, R. L.; Jespersen, T.; Christophersen, P.; Strobaek, D.; Jensen, B. S.; Olesen, S.-P. (NeuroSearch A/S, Ballerup, DK 2750, Den.). Neuropharmacology, 40(7), 888-898 (English) 2001. CODEN: NEPHBW. ISSN: 0028-3908. Publisher: Elsevier Science Ltd..

AB Activation of potassium channels generally reduces cellular excitability, making potassium channel openers potential drug candidates for the treatment of diseases related to hyperexcitability such as epilepsy, neuropathic pain, and neurodegeneration. Two compds., BMS-204352 and retigabine, presently in clin. trials for the treatment of stroke and epilepsy, resp., have been proposed to exert their protective action via an activation of potassium channels. Here we show that KCNQ4 channels, stably expressed in HEK293 cells, were activated by retigabine and BMS-204352 in a reversible and concentration-dependent manner in the concentration range 0.1-10 μM. Both compds. shifted the KCNQ4 channel activation curves towards more neg. potentials by about 10 mV. Further, the maximal current obtainable at large pos. voltages was also increased concentration-dependently by both compds. Finally, a pronounced slowing of the deactivation kinetics was induced in particular by BMS-204352. The M-current blocker linopirdine inhibited the baseline current, as well as the BMS-204352-induced activation of the KCNQ4 channels. KCNQ2, KCNQ2/Q3, and KCNQ3/Q4 channels were activated to a similar degree as KCNQ4 channels by 10 μM of BMS-204352 and retigabine, resp. The compds. are, thus, likely to be general activators of M-like currents.

IT **187523-35-9**, BMS-204352
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KCNQ4 channel activation by BMS-204352 and retigabine)

RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 15 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

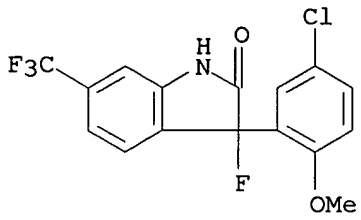
2001:268720 Document No. 135:102442 Targeting acute ischemic stroke with a calcium-sensitive opener of maxi-K potassium channels. Gribkoff, Valentin K.; Starrett, John E., Jr.; Dworetzky, Steven I.; Hewawasam, Piyasena; Boissard, Christopher G.; Cook, Deborah A.; Frantz, Stephen W.; Heman, Karen; Hibbard, Jeffrey R.; Huston, Kevin; Johnson, Graham; Krishnan, Bala S.; Kinney, Gene G.; Lombardo, Lynn A.; Meanwell, Nicholas A.; Molinoff, Perry B.; Myers, Robert A.; Moon, Sandra L.; Ortiz, Astrid; Pajor, Lorraine; Pieschl, Rick L.; Post-Munson, Debra J.; Signor, Laura J.; Srinivas, Nugehally; Taber, Matthew T.; Thalody, George; Trojnacki, Joanne T.; Wiener, Harvey; Yeleswaram, Krishnaswamy; Yeola, Sarita W. (Neuroscience Drug Discovery, Bristol-Myers Squibb Pharmaceutical Res. Inst., Wallingford, CT, USA). Nature Medicine (New York, NY, United States), 7(4), 471-477 (English) 2001. CODEN: NAMEFI. ISSN: 1078-8956. Publisher: Nature America Inc..

AB During ischemic stroke, neurons at risk are exposed to pathol. high levels of intracellular calcium (Ca++), initiating a fatal biochem. cascade. To protect these neurons, the authors have developed openers of large-conductance, Ca++-activated (maxi-K or BK) potassium channels, thereby augmenting an endogenous mechanism for regulating Ca++ entry and membrane potential. The novel fluoro-oxindoles BMS-204352 and its racemic compound are potent, effective and uniquely Ca++-sensitive openers of maxi-K channels. In rat models of permanent large-vessel stroke, BMS-204352 provided significant levels of cortical neuroprotection when administered two hours after the onset of occlusion, but had no effects on blood pressure or cerebral blood flow. This novel approach may restrict Ca++ entry in neurons at risk while having minimal side effects.

IT **183720-28-7 187523-35-9**, BMS-204352
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting acute ischemic stroke with fluoro-oxindole calcium-sensitive opener of maxi-K potassium channels to restrict calcium entry)

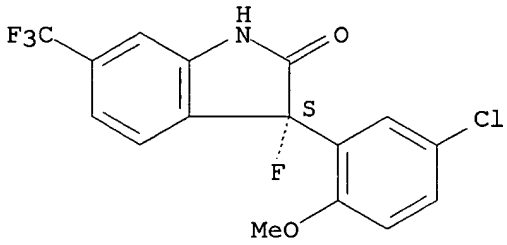
RN 183720-28-7 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



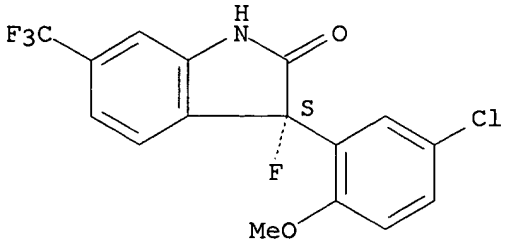
RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 16 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:258389 Document No. 135:174557 BMS-204352: Treatment of stroke with potassium (Maxi-K) channel opener. Sorbera, L. A.; Martin, L.; Castaner, J.; Castaner, R. M. (Prous Science, Barcelona, 08080, Spain). Drugs of the Future, 26(1), 9-14 (English) 2001. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.
AB A review with 19 refs. regarding the potassium (Maxi-K) channel opener BMS-204352 and its use for the treatment of stroke. Topics discussed include its synthesis, description, pharmacol. actions, and clin. studies.
IT **187523-35-9**, BMS-204352
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(BMS-204352 as potassium (Maxi-K) channel opener for treatment of stroke in relation to pharmacokinetics and toxicity)
RN 187523-35-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 17 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2001:247176 Document No. 134:262198 Treatment of carbon monoxide poisoning. Gilmer, Benjamin P.; Tomaszewski, Christian; Watts, John A., Jr. (Charlotte-Mecklenburg Hospital Authority Doing Business as Carolinas Medical Center, USA). PCT Int. Appl. WO 2001022960 A1 20010405, 21 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US41016 20000928. PRIORITY: US 1999-PV157198 19990930.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001022960	A1	20010405	WO 2000-US41016	20000928

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AB It has been discovered that neuromodulators may be used in the treatment of severe carbon monoxide (CO) poisoning. These neuromodulators include those that prevent the release of excitatory neurotransmitters, such as riluzole, and mols. that competitively and non-competitively antagonize glutamate receptors, particularly of the NMDA type. Another class of neuromodulators that are useful in the treatment of carbon monoxide poisoning includes adenosine and its derivs. that have a binding affinity for the A1 or A2 receptors, such as N-cyclochloro-P-adenosine (CCPA). Also included are mols. that modulate adenosine transport and metabolism by either inhibiting adenosine deaminase or adenosine kinase or nucleoside transporters. Another effective class of neuromodulators includes arginine derivative that inhibit nitric oxide synthetase (NOS), such as L-nitro-arginine-methyl-ester (L-NAME). Another class of therapeutic drugs includes antioxidants such as DMSO. Another class of neuroprotective agents that are effective in treating carbon monoxide poisoning includes mols. that inhibitor poly(ADP-ribose) polymerase (PARP), such as 3-aminobenzamide and 5-aminoisoquinolinone. Finally,

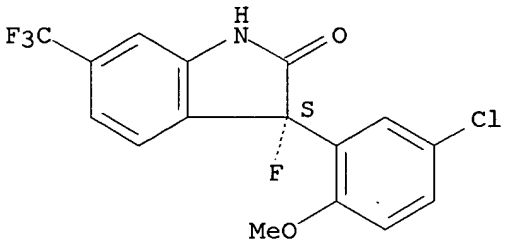
another class of neuromodulatory agents includes mols. such that open potassium channels, particularly of the maxi K+ channel type, such as BMS 204352.

IT **187523-35-9**, BMS 204352
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of carbon monoxide poisoning)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 18 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2003:121867 Document No. 139:223420 BMS-204352: a potassium channel opener developed for the treatment of stroke. Jensen, Bo Skaaning (Section of Ion Channel Pharmacology, NeuroSearch A/S, Ballerup, Den.). CNS Drug Reviews, 8(4), 353-360 (English) 2002. CODEN: CDREFB. ISSN: 1080-563X. Publisher: Neva Press.

AB A review. During ischemic stroke, a fatal biochem. cascade that results in neuronal hyperexcitability is initiated when neurons at risk are exposed to excessive excitatory amino acids and pathol. high levels of intracellular calcium (Ca2+). Therefore, neuroprotectants including NMDA-antagonists and blockers of voltage-gated Ca2+ channels have been proposed as novel strategies for stroke treatment. Since potassium channels are key players in the control of neuronal excitability, and activation of neuronal potassium channels decrease excitability and neurotransmitter release, a novel approach for targeting acute ischemic stroke has been to develop openers of neuronal potassium channels. Bristol-Myers Squibb is developing BMS-204352, a fluoro-oxindole potassium channel opener, as a potential neuroprotectant for the treatment of acute ischemic stroke. BMS-203252 is a potent and effective opener of two important subtypes of neuronal potassium channels, the calcium-activated, big-conductance potassium channels (KCa channels) and voltage-dependent, non-inactivating potassium channels known as KCNQ channels. BMS-204352 (0.3 mg/kg, i.v.) significantly reduced cortical infarct volume in a model of permanent occlusion of the middle cerebral artery (MCA) in spontaneous hypertensive rats (SHR), as compared to vehicle when administered 2 h post-occlusion. At doses from 1 μg/kg to 1 mg/kg i.v., BMS-204352 produced a significant reduction in cortical infarct volume in normotensive Wistar rats. In healthy humans, single and multiple i.v. doses of BMS-204352 (0.001 to 0.2 mg/kg) were safe, well-tolerated and without psychomotor function effects. Multiple doses of BMS-204352 (0.1-2 mg/kg i.v.) administered within 48 h after stroke onset were well tolerated in patients in Phase II studies, designed to evaluate safety, tolerability and pharmacokinetics. No clin. significant differences in organ toxicity or adverse effects were found, and total clearance and volume of

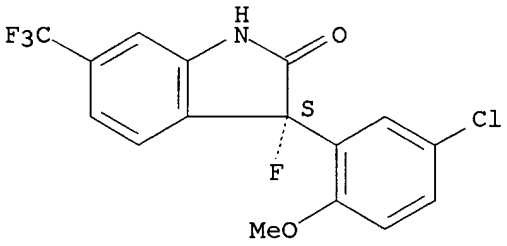
distribution were independent of dose. BMS-204352 failed to show superior efficacy in acute stroke patients compared to placebo in a Phase III study that included 1978 patients at 200 centers worldwide.

IT **187523-35-9**, BMS-204352
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMS-204352, potassium channel opener developed for treatment of stroke)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 19 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2002:899341 Document No. 139:78101 Advances in technologies for the discovery and characterization of ion channel modulators: focus on potassium channels. Gribkoff, Valentin K.; Starrett, John E., Jr. (Neuroscience Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, 06492, USA). Annual Reports in Medicinal Chemistry, 37, 237-246 (English) 2002. CODEN: ARMCBI. ISSN: 0065-7743. Publisher: Elsevier Science.

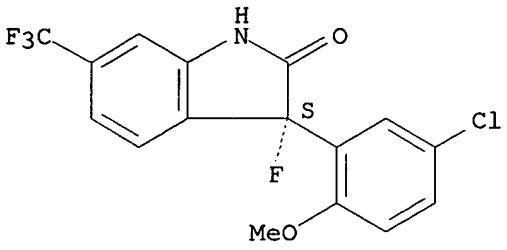
AB A review on recent developments in technologies for the discovery and characterization of effective K+ channel modulators. Mol. cloning has identified a large number of unique K+ channels, which have played a key role in expanding the ability to search for channel-specific modulators. Advances in electrophysiol. techniques have allowed the development of higher throughput assays to directly visualize the effects of modulators on specific channel currents. Structure-activity relationship studies in relation to specific K+ channels have enabled the creation of directed chemical libraries rich in K+ channel modulators tractable to combinatorial synthesis.

IT **187523-35-9**, Bms-204352
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(advances in technol. for discovery and characterization of potassium ion channel modulators)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

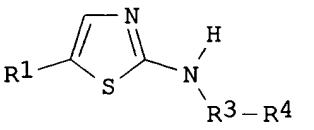
Absolute stereochemistry. Rotation (+).



L8 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2002:866687 Document No. 137:353013 Thiazole derivatives and their use as cdk inhibitors, including combinations and pharmaceutical compositions. Cooper, Christopher Blair; Helal, Christopher John; Sanner, Mark Allen (Pfizer Products Inc., USA). Eur. Pat. Appl. EP 1256578 A1 20021113, 32 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2002-253106 20020502. PRIORITY: US 2001-PV290466 20010511.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1256578	A1	20021113	EP 2002-253106	20020502
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2002338556	A2	20021127	JP 2002-132275	20020508
BR 2002001691	A	20030311	BR 2002-1691	20020513
US 2003078252	A1	20030424	US 2002-144403	20020513

GI



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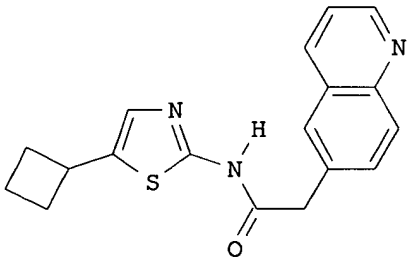


II

AB The invention provides compds. thiazole derivs. I [wherein: R1 = (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, bicycloalkyl, bicycloalkenyl, heterobicycloalkyl, aryl, heteroaryl, or amino including cyclic amino; R3 = (un)substituted CONH, COO, CO(CH2)n, (CH2)n; R4 = as given for R1 except amino; n = 0-3; including pharmaceutically acceptable salts]. I are inhibitors of cyclin-dependent protein kinases (cdk), particularly cdk5, cdk2, and GSK-3. Pharmaceutical compns. and methods comprising compds. I are described, particularly for treating diseases and conditions comprising abnormal cell growth, such as cancer, and neurodegenerative diseases and conditions and those affected by dopamine neurotransmission. Also described are pharmaceutical compns. and methods comprising compds. I for treating or improving the following: male fertility and sperm motility

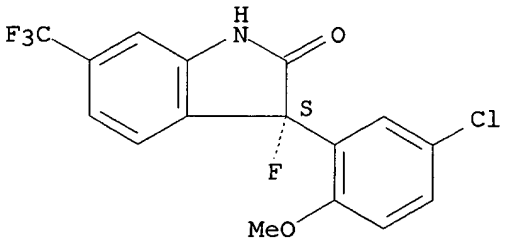
problems, diabetes mellitus, impaired glucose tolerance, metabolic syndrome or syndrome X, polycystic ovary syndrome, adipogenesis and obesity, myogenesis and frailty (for example age-related decline in phys. performance), acute sarcopenia (for example, muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery), sepsis, hair loss, hair thinning, balding, and immunodeficiency. Approx. 90 specific compds. I are claimed, and the prepns. of 5 of these and several intermediates are exemplified. For instance, 2-aminothiazole was lithiated and silylated, then re-lithiated and treated with cyclobutanone to give 1-(2-aminothiazol-5-yl)cyclobutanol. This alc. was hydrogenated to give 5-cyclobutylthiazol-2-ylamine, which was coupled with 6-quinolylacetic acid using T3P (1-propanephosphonic acid cyclic trimeric anhydride), to give title compound II. The 5 exemplified compds. all had IC50 values of < 50 μM for inhibiting cdk5, cdk2, and GSK-3β in vitro.

IT **187523-35-9**, BMS-204352
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutics also containing; preparation of thiazole derivs. as cdk inhibitors)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 21 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2002:793402 Document No. 137:289015 Methods using KCNQ potassium channel agonists for treating hyperactive gastric motility. Argentieri, Thomas Michael (Wyeth, John, and Brother Ltd., USA). PCT Int. Appl. WO 2002080898 A2 20021017, 24 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US10268 20020402. PRIORITY: US 2001-PV281471 20010404.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002080898	A2	20021017	WO 2002-US10268	20020402
	WO 2002080898	A3	20030821		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

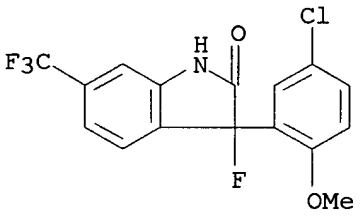
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002183395 A1 20021205 US 2002-114148 20020402

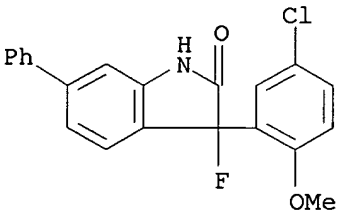
AB The invention provides methods and pharmaceutical compns. for treating, inhibiting, or preventing hyperactive gastric motility in a mammal, using agonists of KCNQ potassium channels, including KCNQ2, KCNQ3, KCNQ4 and KCNQ5 potassium channels, alone or in combination. The hyperactive gastric motility may be associated with maladies including colitis, irritable bowel syndrome, and Crohn's disease. Compds. useful in these methods include the 1,2,4-triaminobenzene derivs. described in U.S. Patent Number 5,384,330 (Dieter et al.) and the substituted 3-Ph oxindole compds. described in U.S. Patent Number 5,565,483 (Hewawasam et al.). Among the preferred compds. of this invention is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid Et ester, also referred to as retigabine.

IT **183720-28-7 183720-32-3 183720-33-4**
183720-35-6 183720-37-8 183720-38-9
187523-41-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KCNQ potassium channel agonists for treating hyperactive gastric motility)

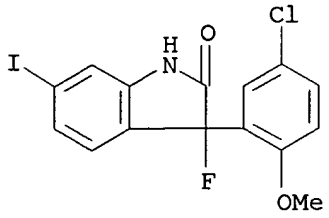
RN 183720-28-7 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



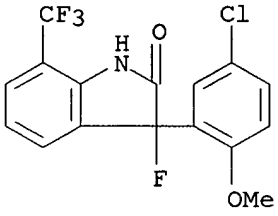
RN 183720-32-3 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-phenyl- (9CI) (CA INDEX NAME)



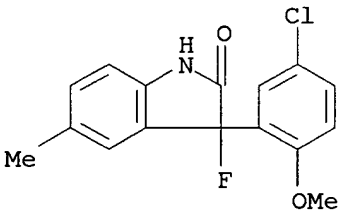
RN 183720-33-4 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-iodo- (9CI) (CA INDEX NAME)



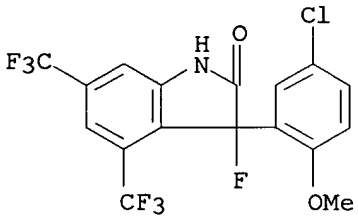
RN 183720-35-6 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-7-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 183720-37-8 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-5-methyl- (9CI) (CA INDEX NAME)

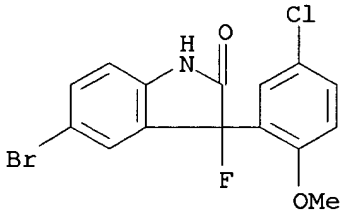


RN 183720-38-9 CAPLUS
CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-4,6-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 187523-41-7 CAPLUS

CN 2H-Indol-2-one, 5-bromo-3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



L8 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2002:753502 Document No. 138:265102 Pharmacokinetics and dose proportionality of BMS-204352 after intraarterial administration to rats. Krishna, Rajesh; Shah, Vinod R.; Srinivas, Nuggehally (Clinical Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA). Biopharmaceutics & Drug Disposition, 23(6), 233-237 (English) 2002. CODEN: BDDID8. ISSN: 0142-2782. Publisher: John Wiley & Sons Ltd..

AB BMS-204352 is a novel maxi-K channel opener that is being developed for the treatment for stroke. The current study was designed to evaluate the dose proportionality and pharmacokinetics of BMS-204352 in rats. In an open, parallel fashion, sixteen rats per gender received a single intraarterial dose of BMS-204352 as a 3-min infusion into the carotid artery at 0.4, 2.0, 5.0 and 10.0 mg/kg dose levels. Serial blood samples were collected for up to 24 h post-dose and plasma samples were analyzed for the concns. of intact BMS-204352 using a validated liquid chromatog. mass spectrometric (LC/MS) method. Pharmacokinetic anal. was performed using a non-compartmental method. Results revealed a gender difference in the pharmacokinetics of BMS-204352 in rats at all doses excluding the first (i.e., 0.4 mg/kg) dose panel. BMS-204352 peak plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) values increased in a proportion greater than the increment in dose. Specifically, as dose increased in the ratio 1:5:12.5:25, Cmax increased in the ratio 1:7:18:31 in male rats and 1:7:22:51 in female rats. The resp. AUC ratios were 1:6:20:42 in male rats and 1:12:29:77 in female rats. Mean total body clearance (CLT) values for BMS-204352 ranged from 879-3242 mL/h/kg over the four dose levels and generally decreased with increase in dose. Similarly, steady state volume of distribution (VSS) values ranged from 3621-8933 mL/kg over the four dose levels and generally decreased with increase in dose. However, mean residence time (MRT) and elimination half-life (T1/2) values for BMS-204352 were independent of dose and ranged from 2.42-4.54 to 2.08-4.70 h, resp. In conclusion, BMS-204352 appears to exhibit dose-dependent pharmacokinetics in rats. In addition, there appeared to be some evidence of gender related differences in the pharmacokinetics of BMS-204352.

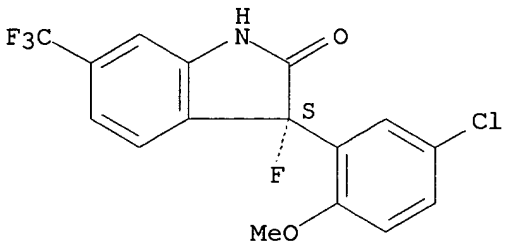
IT **187523-35-9**, BMS-204352
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics and dose proportionality of BMS-204352 after intraarterial administration to rats)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-

(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 23 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

2002:753501 Document No. 138:265101 Effect of dose and input rate on the brain penetration of BMS-204352 following intravenous administration to rats. Krishna, Rajesh; Palme, Holly; Zeng, Jianing; Srinivas, Nuggehally (Clinical Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA). Biopharmaceutics & Drug Disposition, 23(6), 227-231 (English) 2002. CODEN: BDDID8. ISSN: 0142-2782. Publisher: John Wiley & Sons Ltd..

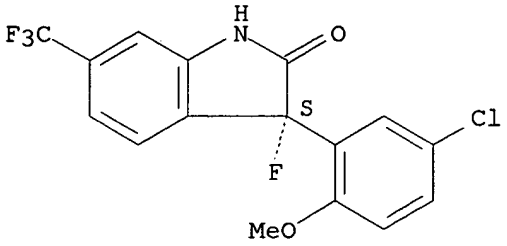
AB BMS-204352 is a novel maxi-K channel opener that is being developed for the treatment for stroke. The current study was designed to evaluate the plasma and brain pharmacokinetics of BMS-204352 in rats, in particular, assessing the effect of dose and input rate on brain penetration of BMS-204352. Rats (3 animals/group/time point) received a single i.v. dose of BMS-204532 as 5 mg/kg bolus, 5 mg/kg 30 min infusion, 5 mg/kg 60 min infusion, and 10 mg/kg bolus dose, into the jugular vein. Terminal blood (for plasma) and brain samples were collected for up to 9 h post-dose and samples were analyzed for the concns. of intact BMS-204352 using a validated liquid chromatog. tandem mass spectrometric method (LC/MS/MS). As dose increased from 5 to 10 mg/kg, both BMS-204352 Cmax and AUC values increased in plasma and brain, somewhat greater in proportion to the increment in dose. Whereas the peak concns. of BMS-204352 were affected by infusion time, overall AUCs were comparable across the bolus and infusion groups. Terminal disposition (T-half ranged from 1.6 to 2.7 h) of BMS-204352 was unaltered as a function of input rate. BMS-204352 crossed the blood-brain barrier with brain-to-plasma (B/P) ratios of approx. 7-11. Brain-to-plasma ratios appeared to be independent of dose and infusions produced somewhat higher brain penetration (B/P of .apprx.11) as compared to bolus (B/P of .apprx.7-8) dose. The decline of BMS-204352 in the brain paralleled that of plasma independent of the input rate and dose.

IT **187523-35-9**, BMS-204352
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(effect of dose and input rate on the brain penetration of BMS-204352 following i.v. administration to rats)

RN 187523-35-9 CAPLUS

CN 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L8 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2002:696658 Document No. 137:210975 Modulators of KCNQ potassium channels and use thereof in treating migraine and mechanistically related diseases. Dworetzky, Steven I.; Gribkoff, Valentin K.; Kinney, Gene G.; Hewawasam, Piyasena (USA). U.S. Pat. Appl. Publ. US 2002128277 A1 20020912, 22 pp. (English). CODEN: USXXCO. APPLICATION: US 2002-75703 20020214. PRIORITY: US 2001-PV269967 20010220.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002128277	A1	20020912	US 2002-75703	20020214
WO 2002072088	A2	20020919	WO 2002-US4374	20020214

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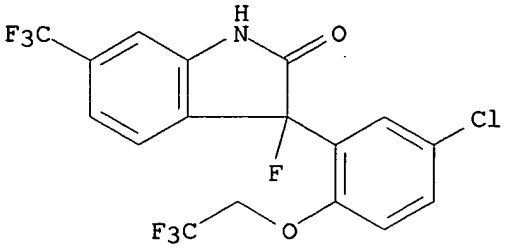
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AB Compds. which function as modulators, particularly, openers, of human KCNQ potassium channel proteins or polypeptides, particularly, central nervous system (CNS)-located KCNQ potassium channels, and heteromultimers thereof, and their use in the treatment of migraine are provided by the present invention. One novel type of potassium channel polypeptide openers provided by the present invention is the fluorooxindole compds., described for the first time as therapeutics for the treatment of migraine by preventing the asynchronous firing of neurons. Other KCNQ potassium channel opener compds. that are also useful in the treatments of the invention include 2,4-disubstituted pyrimidine-5-carboxamide derivs. One or more of the compds. according to the present invention may be utilized alone, in combination, or in conjunction with other treatment modalities for reducing, ameliorating and/or alleviating migraine or diseases similar to, or mechanistically related to, migraine, e.g., cluster headache.

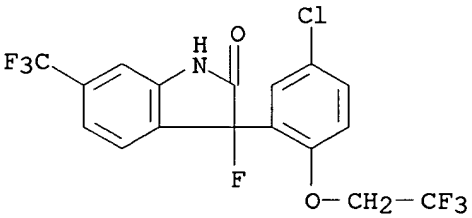
IT **452082-81-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modulators of KCNQ potassium channels and use thereof in treating migraine and mechanistically related diseases)

RN 452082-81-4 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



IT **452082-80-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(modulators of KCNQ potassium channels and use thereof in treating migraine and mechanistically related diseases)
RN 452082-80-3 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
2002:658077 Document No. 137:201228 Preparation of 3-fluoro-3-phenyloxindole derivatives as modulators of KCNQ potassium channels for treatment of migraines. Hewawasam, Piyasena; Dextraze, Pierre; Gribkoff, Valentin K.; Kinney, Gene G.; Dworetzky, Steven I. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2002066426 A2 20020829, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US4304 20020214. PRIORITY: US 2001-PV270112 20010220.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002066426	A2	20020829	WO 2002-US4304	20020214
WO 2002066426	A3	20021121		

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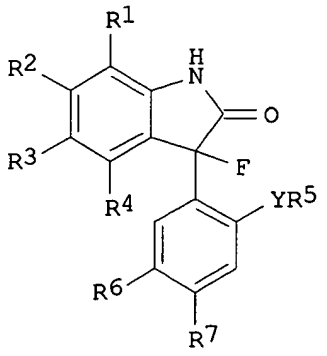
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 6469042 B1 20021022 US 2002-75522 20020214

US 2002156120 A1 20021024

GI



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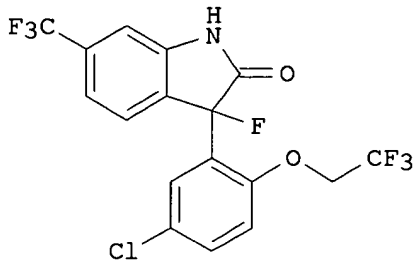


II

AB Title compds. I [wherein R1, R2, R3 and R4 = independently H, alkyl, halo, CH2F, CF3, Ph, 4-MeC6H4, or 4-CF3C6H4; R5 = alkyl optionally substituted with 1-3 F or Cl, provided R5 ≠ alkyl when Y = O; Y = O or S; R6 and R7 = independently H, Cl, Br, or CF3; stereoisomers thereof] were prepared as openers of the KCNQ K+ channels. For example, 6-(trifluoromethyl)isatin was converted to the Na salt and then treated with 5-chloro-2-(2,2,2-trifluoroethoxy)phenylmagnesium bromide to give the 1,3-dihydro-3-hydroxy-3-phenyl-2H-indol-2-one derivative (70%). Fluorination using Et2NSF3 afforded II (93%), which increased whole-cell outward K+ KCNQ-mediated currents in Xenopus oocytes by > 150% over controls at 10 μM. I are useful in the treatment of disorders which are responsive to the opening of the KCNQ K+ channels, such as migraine (no data).

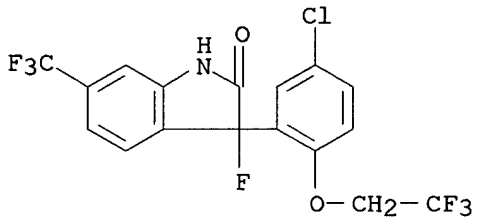
IT **452082-80-3P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452082-91-6P**, 6-Chloro-3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-1,3-dihydro-3-fluoro-2H-indol-2-one

RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

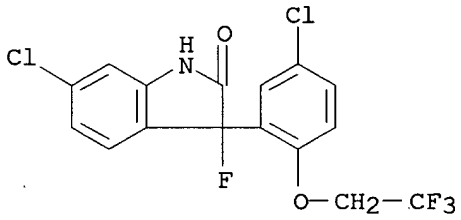
(KCNQ potassium channel modulator; preparation of fluorophenyloxindole derivs. as modulators of KCNQ potassium channels for treatment of migraines)

RN 452082-80-3 CAPLUS

CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



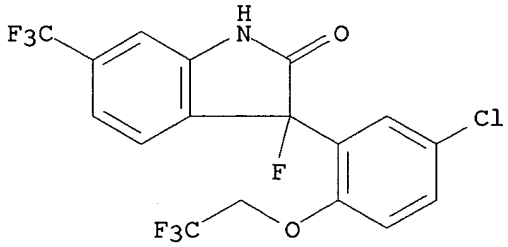
RN 452082-91-6 CAPLUS
CN 2H-Indol-2-one, 6-chloro-3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



IT **452082-81-4P 452082-82-5P 452082-92-7P 452082-93-8P**
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(KCNQ potassium channel modulator; preparation of fluorophenyloxindole derivs. as modulators of KCNQ potassium channels for treatment of migraines)

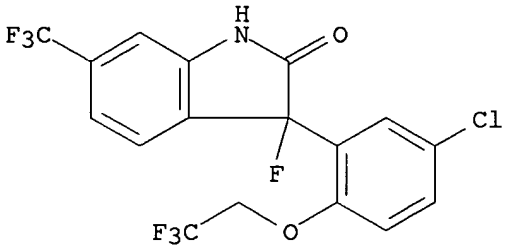
RN 452082-81-4 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



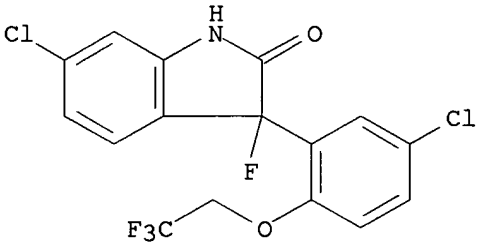
RN 452082-82-5 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



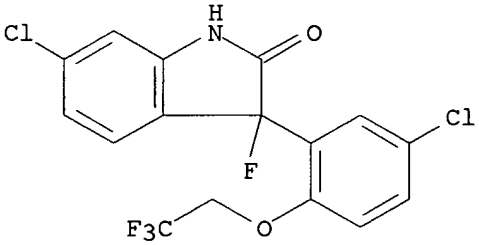
RN 452082-92-7 CAPLUS
CN 2H-Indol-2-one, 6-chloro-3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



RN 452082-93-8 CAPLUS
CN 2H-Indol-2-one, 6-chloro-3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-, (-)- (9CI) (CA INDEX NAME)

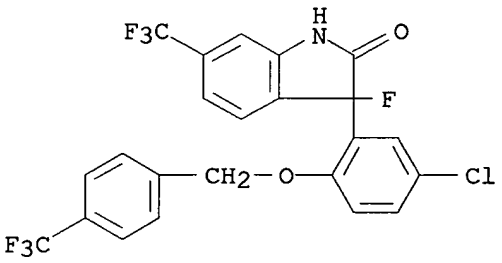
Rotation (-).



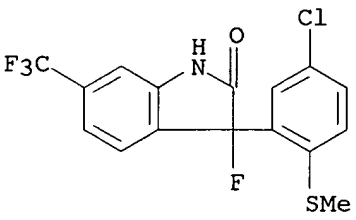
IT **452082-83-6P**, 3-[5-Chloro-2-[[4-(trifluoromethyl)phenyl]methoxy]phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one **452082-84-7P**, 3-(5-Chloro-2-methylthiophenyl)-3-fluoro-6-trifluoromethyl-1,3-dihydroindol-2-one **452082-86-9P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-1,3-dihydro-3,6-difluoro-2H-indol-2-one **452082-87-0P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-1,3-dihydro-3-fluoro-6-(fluoromethyl)-2H-indol-2-one **452082-88-1P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-4,6-dichloro-1,3-dihydro-3-fluoro-2H-indol-2-one **452082-89-2P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-5,6-dichloro-1,3-dihydro-3-fluoro-2H-indol-2-one **452082-90-5P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-1,3-dihydro-3,5,6-trifluoro-2H-indol-2-one

452082-95-0P, 3-[5-Chloro-2-(2-fluoroethoxy)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452082-96-1P**, 3-[4,5-Dichloro-2-(2-fluoroethoxy)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452082-97-2P**, 3-[5-Chloro-2-(2-fluoroethylthio)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452082-98-3P**, 3-[5-Chloro-2-(ethylthio)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452082-99-4P**, 3-[5-Chloro-2-[(2-methylphenylmethyl)thio]phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452083-00-0P 452083-01-1P**, 3-[5-Chloro-2-(propylthio)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452083-02-2P**, 3-[5-Chloro-2-(2,5-difluorophenylmethylthio)phenyl]-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one **452083-03-3P 452083-04-4P**, 3-[5-Chloro-2-(2,2,2-trifluoroethoxy)phenyl]-1,3-dihydro-3-fluoro-6-[4-(trifluoromethyl)phenyl]-2H-indol-2-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(KCNQ potassium channel modulator; preparation of fluorophenyloxindole derivs. as modulators of KCNQ potassium channels for treatment of migraines)

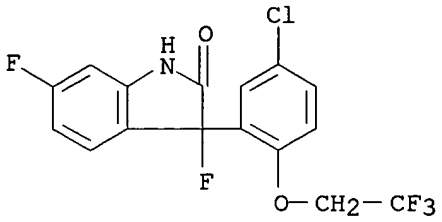
RN 452082-83-6 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-[[4-(trifluoromethyl)phenyl]methoxy]phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



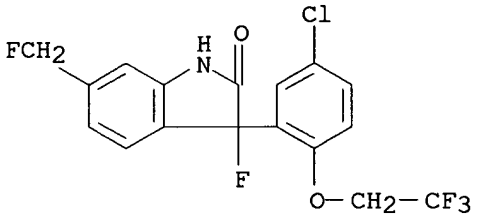
RN 452082-84-7 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(methylthio)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



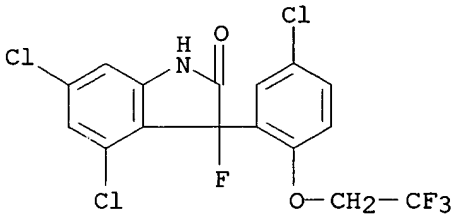
RN 452082-86-9 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3,6-difluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



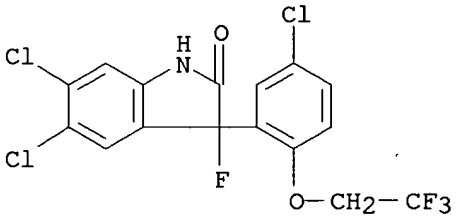
RN 452082-87-0 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-6-(fluoromethyl)-1,3-dihydro- (9CI) (CA INDEX NAME)



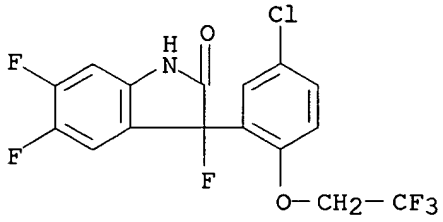
RN 452082-88-1 CAPLUS
CN 2H-Indol-2-one, 4,6-dichloro-3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



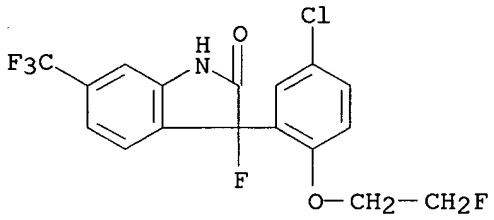
RN 452082-89-2 CAPLUS
CN 2H-Indol-2-one, 5,6-dichloro-3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



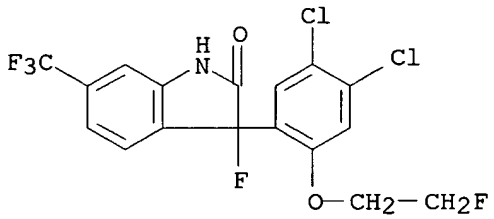
RN 452082-90-5 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3,5,6-trifluoro-1,3-dihydro- (9CI) (CA INDEX NAME)



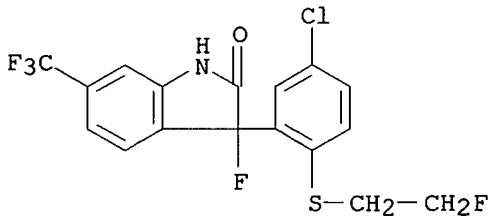
RN 452082-95-0 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2-fluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 452082-96-1 CAPLUS
CN 2H-Indol-2-one, 3-[4,5-dichloro-2-(2-fluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)

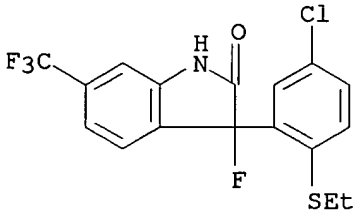


RN 452082-97-2 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-[(2-fluoroethyl)thio]phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)

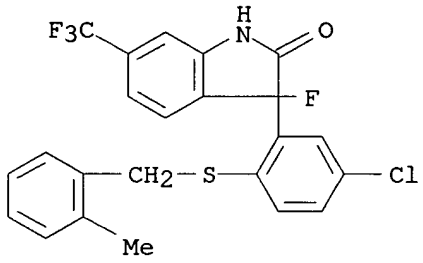


RN 452082-98-3 CAPLUS

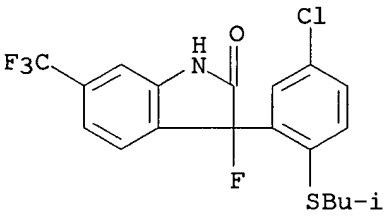
CN 2H-Indol-2-one, 3-[5-chloro-2-(ethylthio)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



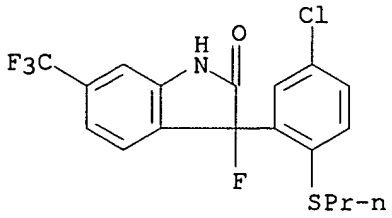
RN 452082-99-4 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-[[(2-methylphenyl)methyl]thio]phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



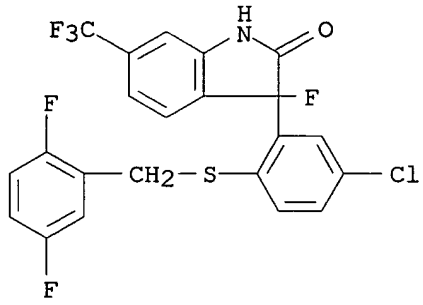
RN 452083-00-0 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-[(2-methylpropyl)thio]phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



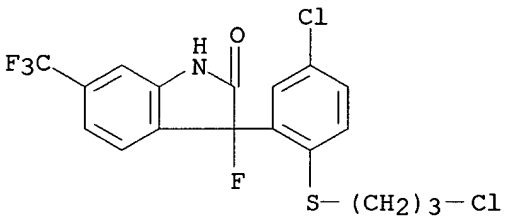
RN 452083-01-1 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(propylthio)phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



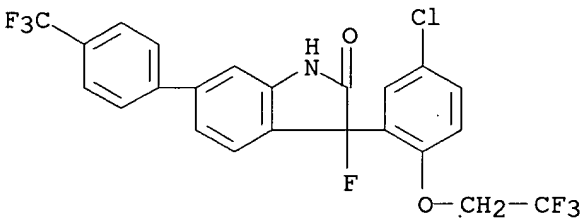
RN 452083-02-2 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-[[(2,5-difluorophenyl)methyl]thio]phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 452083-03-3 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-[(3-chloropropyl)thio]phenyl]-3-fluoro-1,3-dihydro-6-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 452083-04-4 CAPLUS
CN 2H-Indol-2-one, 3-[5-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-3-fluoro-1,3-dihydro-6-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:.
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   117.57     414.48

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                   -16.28     -16.28

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